Peri-Operative Use of Injectable Rimadyl®
(carprofen)

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Key Points

• Since inflammation is a driving factor in the development of surgical pain, the anti-inflammatory properties of Rimadyl® (carprofen) make this drug an important component of a post-operative pain management protocol.

• Preemptive pain management, followed by appropriate intra-operative and post-operative analgesia, can circumvent central sensitization and prevent the onset of chronic, intractable pain.

• Rimadyl is the only NSAID developed in the US specifically for canine use and is available as oral caplet, chewable tablet, and sterile injectable (SC) formulations. All formulations have the same indications:
  – relief of pain and inflammation associated with osteoarthritis;
  – control of post-operative pain associated with soft tissue and orthopedic procedures.

• Rimadyl is the only injectable NSAID approved by the FDA for controlling post-operative pain in the dog that is supported by greater than 10 years of research.

• Rimadyl Injectable can be administered at 4.4 mg/kg (2.0 mg/lb) SC before surgery as part of a balanced, multimodal anesthesia/analgesia protocol, providing 24 hours of analgesia. After surgery, patients can be easily transitioned to oral Rimadyl since no wash-out period is required between use of the injectable and oral Rimadyl.

• Clinical and pharmacokinetic studies support the benefits of administering Rimadyl Injectable preoperatively to control post-operative pain in dogs, as dogs that received Rimadyl prior to surgery had better immediate post-operative analgesia than dogs that received Rimadyl after surgery.

• The mechanism of action that allows NSAIDs to provide effective analgesia may also be responsible for adverse reactions in some patients. Although adverse events associated with Rimadyl Injectable are rare, patient selection is essential to ensure favorable outcomes. In stable canine patients, the benefits of administering Rimadyl Injectable preoperatively outweigh the risks and will provide up to 24 hours of analgesia.
INTRODUCTION AND RATIONALE

The effects of non-steroidal anti-inflammatory drugs (NSAIDs) are exerted through the inhibition of cyclooxygenase (COX) enzymes and the subsequent synthesis of prostaglandins. As key components of inflammation, prostaglandins contribute to the generation of pain by synergistically interacting with other inflammatory mediators. Thus, the analgesic effects of NSAIDs are mediated through inhibition of COX enzymes and prostaglandin synthesis.

Rimadyl® (carprofen) was the first NSAID developed in the US specifically for use in the dog. The original oral tablet formulation was approved by the FDA in 1996, followed by approval of the highly palatable chewable tablet in 1999. Rimadyl Injectable sterile solution was approved in 2003 and is labeled for subcutaneous (SC) injection. Both formulations can be administered as a single daily dose of 4.4 mg/kg body weight (2.0 mg/lb) or divided into twice-daily doses at 2.2 mg/kg (1.0 mg/lb). Although extensive studies have not been conducted to evaluate consecutive use of different NSAIDs, a wash-out period is recommended when changing from one NSAID to another.² By using Rimadyl Injectable pre-operatively, followed by oral Rimadyl post-operatively, continuous and uninterrupted analgesia can be provided throughout surgery and recovery, including the convalescent period after the patient is released from the hospital.

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Rimadyl is the first injectable NSAID, and carprofen is the only injectable NSAID that is FDA approved for controlling post-operative pain in the dog, and is backed by over 10 years of research. Since inflammation is a driving factor in the development of surgical pain, the anti-inflammatory properties of Rimadyl make this drug an important component of a post-operative pain-management protocol:

- Rimadyl Injectable can be administered SC before surgery as part of a balanced, multimodal anesthesia/analgesia protocol. The injectable Rimadyl formulation provides an alternative to use of an oral pre-operative NSAID, especially when the animal is sedated or unresponsive, intractable, or at risk of emesis (e.g., due to an anesthetic drug), or for other situations where oral medications are not an option.
- After surgery, patients can be easily transitioned to oral Rimadyl since no wash-out period is required between use of the injectable and oral Rimadyl formulations.

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COX-2:
- Is an inducible enzyme (i.e., only present during pathological conditions such as inflammation) which is up-regulated after arachidonic acid is released as a result of cell injury and initiates a cascade of events that results in synthesis of pro-inflammatory prostaglandins such as prostaglandin E2 (PGE\(_2\)) and prostacyclin (PGI\(_2\)).
- Is constitutively expressed in the kidney and, through PGE\(_2\) production, regulates sodium and water absorption.
- Is up-regulated during renal ischemia, leading to synthesis of PGE\(_2\) and PGI\(_2\), both potent vasodilators that maintain renal blood flow of the proximal renal artery to preserve glomerular filtration rate in hypovolemic or hypotensive patients.\(^6\)\(^8\)
- May play a role in renal development (COX-2-deficient mice have been shown to develop severe renal dysplasia).\(^9\)
- Plays a cytoprotective role in the GI tract. Although not involved in maintaining GI homeostasis in the normal healthy GI tract, COX-2 enzymes are up-regulated in gastric inflammation and play an important role in healing gastric ulcers.\(^10\)

When the first NSAIDs such as aspirin and indomethacin were developed, the roles of the two COX enzymes were unknown. These drugs indiscriminately inhibited both COX-1 and COX-2 enzymes, and although effective as analgesics, the drugs had significant adverse-event profiles which limited their use. As it became clear that COX-1 was constitutive and COX-2 was primarily involved in inflammation, newer COX-1-sparing NSAIDs were developed. The goal was to selectively inhibit the inflammatory activity of COX-2 enzymes while preserving the ‘housekeeping’ or homeostatic activities of COX-1 enzymes in an effort to minimize adverse effects.

However, as the cytoprotective effects of the COX-2 enzymes were discovered, the need to balance COX-2 inhibition became apparent. The currently available FDA-approved veterinary NSAIDs selectively inhibit COX-2 to a greater extent than COX-1 in varying degrees. \(\text{In vitro}\) studies have been conducted to determine the difference in COX-2 and COX-1 enzyme inhibition of these drugs, in an effort to predict their clinical efficacy and safety profiles.\(^11\)\(^-\)\(^15\) Results of these assays have been variable and the clinical relevance has not been established. Therefore, \(\text{in vitro}\) assays evaluating COX inhibition by an NSAID are not reliably predictive of efficacy or safety. Rather, the efficacy and safety of an NSAID can only be determined by robust clinical studies.\(^16\)

Studies that have investigated the efficacy and safety of canine NSAIDs, combined with their clinical history, have demonstrated that all approved veterinary NSAIDs are safe and effective when used according to label recommendations. Clear-cut distinctions in the performance of these NSAIDs have not been observed in the general population of dogs, but individual patients may better tolerate one NSAID over another.\(^17\) Maximizing the benefits and minimizing the risks of any NSAID used in an anesthesia protocol should involve appropriate patient selection, assessing the level of analgesia required, supporting the patient during surgery to maintain vital organ function, monitoring the patient’s response, and accordingly adjusting the patient’s environment.

‘PAIN’ OVERVIEW
As potent anti-inflammatory drugs, NSAIDs are routinely used in human and veterinary medicine to control post-operative pain. The following graphics and discussion summarizes key concepts that need to be considered for managing the pain of a surgical patient. An overview of the pain pathway (Figure 1), the various types of pain, and the role that inflammation plays in initiating surgical pain (Figure 2) is helpful to better understand the analgesic effects of NSAIDs.

Pain Pathway
The pain pathway (Figure 1) has four distinct stages, starting with transduction and ending with perception. Drug therapies have been developed to interfere with pain transmission at each of these stages. NSAID effects occur at transduction and modulation.

Responses to Pain
Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Several responses to pain ensue once a peripheral pain signal has been initiated.
A. **Withdrawal reflex:** The peripheral sensory neuron synapses with interneurons within the spinal cord, which synapse with efferent motor neurons in the ventral horn to stimulate flexor muscles and initiate a withdrawal reflex. The withdrawal reflex occurs simultaneously with projection of the pain signal to the brain. This explains the unconscious withdrawal response that occurs concurrently with the acknowledgement of the pain sensation.19

B. **Neurogenic inflammation:** As illustrated in Figure 3, neurogenic inflammation involves a positive feedback mechanism whereby the peripheral sensory neuron releases neurotransmitters in a retrograde manner, back to the area of inflammation, and stimulate release of prostaglandins and other inflammatory mediators. Neurogenic inflammation can become part of a progressive cycle of inflammation and tissue damage that maintains the release of inflammatory mediators and contributes to peripheral and central sensitization.20

C. **Descending pathway modulation:** Once the pain signal reaches the brain, descending pathways can be inhibitory (providing analgesia) or excitatory (exacerbating pain), further modulating the sensation of pain.

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**Pathological Pain**

Pain can be categorized as either: 1) **physiological pain,** also known as nociceptive pain (see below); or 2) **pathological pain,** which includes:

- inflammatory pain (due to tissue damage);
- chronic pain or maladaptive pain;
- neuropathic pain (due to nerve damage; see below).21

**PHYSIOLOGICAL PAIN:** Physiological pain is the immediate response to a noxious stimulus and is mediated through high-threshold pain receptors located on thinly myelinated Aδ and unmyelinated C nerve fibers.

- Aδ nociceptors are responsible for ‘first pain’ which is typically sharp, localized, and transient.
- C nociceptors conduct pain more slowly and project to larger receptive fields than Aδ nociceptors. Pain associated with C-fiber activation is characterized as ‘second pain’ which has a slow onset, is dull or throbbing, and poorly localized.

Physiological pain is unpleasant, causing the individual to immediately withdraw from the painful stimulus. Physiological pain is a protective mechanism that signals individuals to avoid or reduce exposure to the inciting cause and allows an individual to adapt and interact safely with their environment.

**NEUROPATHIC PAIN:** This type of pain is a result of nerve damage which causes ectopic generation of action potentials. Limb amputation, crushing injuries, and endocrinopathies (e.g., diabetes mellitus, hepatic neuritis) are conditions associated with neuropathic pain. Similar to chronic inflammatory pain, neuropathic pain is also a maladaptation of the nervous system resulting in central sensitization and manifests as hyperalgesia and allodynia.
Figure 2 – Overview of the role of inflammation in initiating surgical pain.

Tissue damage that occurs after trauma results in a dramatic change of the chemical environment of the Aδ and C nociceptors. The damaged cells, as well as inflammatory cells (mast cells, macrophages, and lymphocytes), release a number of inflammatory mediators, including prostaglandins, bradykinin, histamine, serotonin (5-HT), ATP, and nerve growth factor (NGF), creating an acidic environment known as the “sensitizing soup.” Inflammatory mediators result in heat, swelling, redness, and pain, which are the hallmarks of inflammation. Some of the inflammatory mediators act directly on the nociceptor to initiate a pain signal, while others sensitize these high-threshold nociceptors, lowering the action potential threshold, resulting in peripheral sensitization. Once peripheral sensitization is established, the typically high-threshold nociceptors not only respond to lower threshold stimuli, but also amplify response to those stimuli. Peripheral sensitization establishes a zone of primary hyperalgesia in the area of inflammation. The peripherally sensitized nociceptors, specifically C-fibers, increase the rate of action potentials, resulting in a supranormal release of neurotransmitters such as 1) glutamate, which activates N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; 2) Substance P, which activates Neurokinin-1 (NK-1) receptors; and 3) calcitonin gene-related peptide (CGRP), which activates CGRP receptors. The increased release of neurotransmitters sensitzes the dorsal horn neurons, resulting in central sensitization. Just as with peripheral sensitization, the neurons in the dorsal spinal cord become sensitized to pain signals. Central sensitization involves an alteration of synaptic receptor density, threshold, and activation. Changes associated with central sensitization lead to alldynia and secondary hyperalgesia. Pain associated with central sensitization persists even after the primary pain stimulus resolves.
Inflammatory pain —

Inflammatory pain occurs after tissue trauma (such as surgery) and is a result of cell damage that causes a release of ions and inflammatory mediators (such as prostaglandins, see Figure 2) which sensitize Aδ and C nociceptors. Sensitized nociceptors have a decreased depolarization threshold so that these typically high-threshold nociceptors respond to low-threshold stimuli. This heightened or hypersensitive response to pain stimuli is called peripheral sensitization (Figure 2). Peripheral sensitization also involves activation of 'silent nociceptors', normally inactive C-fiber nociceptors that become activated by inflammatory mediators. Once activated, the silent nociceptors respond to mechanical and thermal stimuli, contributing to peripheral hypersensitization. Therefore, peripheral sensitization results in a hyperactivity to pain both through lowered activation thresholds and recruitment of silent nociceptors.

Peripheral sensitization is clinically manifested as primary hyperalgesia, an exaggerated and prolonged pain response initiated by the sensitization of the Aδ, C, and silent nociceptors located in the area directly affected by tissue damage and inflammation.

Several inflammatory mediators are involved in the development of peripheral sensitization, including those summarized in Figure 2. Though these inflammatory mediators can act independently, they more often work together to create a 'sensitizing soup' that leads to peripheral sensitization.

Peripheral sensitization is reversible, with pain signaling returning to a normal state after the injury resolves. Similar to physiological pain, peripheral sensitization can be a protective and reparative response to tissue damage, initiating behavioral changes that allow an individual to rest and protect the injured area, in order to prevent further injury and facilitate healing.
Central sensitization —

Central sensitization occurs when repetitive firing of sensitized C-fibers causes a constant release of excitatory neurotransmitters within the dorsal horn (Figure 2). Constant bombardment and release of neurotransmitters such as Substance P, calcitonin gene-related peptide (CGRP), and glutamate leads to an increase in the sensitivity of the dorsal horn neurons.27 These neurotransmitters bind to specific receptors in the dorsal horn, including neurokinin-1 receptors, CGRP receptors, N-methyl-D-aspartate (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and contribute to the exaggerated response to pain.27 Central sensitization is not only a result of an increase in excitatory stimulus but can also result from a decreased response to inhibitory neurotransmitters.27

Clinical manifestations of central sensitization include secondary hyperalgesia and allodynia. Secondary hyperalgesia involves a pain sensation that appears to originate outside the area of the damaged tissue and is due to Aδ nerve fiber activation. Allodynia occurs when a light tactile touch results in painful response due to Aβ sensory nerve fiber activation. Although both secondary hyperalgesia and allodynia appear to originate from the periphery, these phenomena are actually generated centrally due to the modification and dynamic changes in processing of input in Aδ fibers and Aβ sensory nerve fibers within the dorsal horn.25-30

Central sensitization occurs concurrently with peripheral sensitization and is also a protective mechanism which is reversible, typically resolving after the injury heals.31 However, when trauma is severe or when pain is allowed to persist or is under-treated, the continued transmission of pain signals to the dorsal horn of the spinal cord can cause continued changes to the dorsal horn neurons, leading to chronic pain or maladaptive pain.

Acute vs Chronic Pain —

Pain has also been classified as acute or chronic. Often, an arbitrary time interval has been used to describe the difference between acute and chronic pain. However, a more accurate description is based on the underlying pathophysiology. Acute pain is associated with a specific injury, and will resolve when the injury heals. In contrast, chronic pain represents a maladaptation to pain and persists after the initial injury resolves. It is a continuation of central sensitization with a drastic alteration in pain processing within the dorsal horn of the spinal cord. The net effect of chronic pain is that pain is no longer associated with the original injury but is now a disease itself, arising spontaneously and resistant to treatment.

COX ENZYMES, PROSTAGLANDINS, AND SENSITIZATION

As mentioned earlier, prostaglandins are among the inflammatory mediators contributing to the development of peripheral and central sensitization associated with inflammatory and chronic pathological pain. Peripherally, in response to tissue damage, COX-2 enzymes are up-regulated, resulting in the synthesis of prostaglandins that contribute to the ‘sensitizing soup’ which leads to peripheral sensitization of the nociceptors. Prostaglandins facilitate the development of peripheral sensitization and primary hyperalgesia by lowering the C and Aδ nociceptor action potential thresholds. Prostaglandins can also activate silent C nociceptors, thus increasing the number of nociceptors involved in pain and further contributing to primary hyperalgesia.32,33

Clinical evidence that COX-2 enzymes and prostaglandins contribute to post-operative pain was demonstrated in a study involving human patients undergoing surgery.34 In this study, an increase in COX-2-derived prostaglandin levels in the peripheral nervous system was correlated with an increased intensity of post-operative pain.

Centrally, COX-1 and COX-2 enzymes are constitutively expressed in the dorsal root ganglia and spinal cord.35 Depolarization of dorsal horn neurons leads to up-regulation of COX-2 and an increase in PGE2 production. PGE2 both facilitates release of neurotransmitters from the primary afferent sensory neuron and decreases the depolarization threshold of the dorsal horn neurons, creating a cycle that perpetuates central sensitization. Additionally, circulating inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β) can also lead to up-regulation of COX-2 in the CNS.36-38
RATIONALE FOR PERI-OPERATIVE NSAIDs

Although general anesthetic drugs render a patient unconscious, these drugs do not interfere with the pathways and processes involved with the development of central sensitization. Therefore, the use of analgesic drugs pre-, intra-, and post-operatively are necessary to adequately address surgical pain. Local anesthetics and systemic analgesics are often used for multimodal analgesia. NSAIDs interfere with both peripheral and central sensitization and provide prolonged analgesia during the post-operative period by inhibiting COX-2 enzymes and prostaglandin production at the surgical site and in the dorsal horn. Clinical studies confirm that NSAID effects on post-operative pain are mediated, at least partially, by interfering with the development of peripheral and central sensitization. Notably, both pre-operative or post-operative administration of Rimadyl has been demonstrated to help reduce peripheral and central sensitization.

Preventive Analgesia Strategy

Preemptive analgesia is the concept of administering pain medication in advance of a painful stimulus in an attempt to block sensitization of nociceptors throughout the peri-operative period. Preventive analgesia, however, broadens the conversation from pre-incisional analgesia to include any analgesic that is administered during the entire peri-operative period. The intent of preventive analgesia is to provide sufficient pain control to prevent development of peripheral and central sensitization. Key concepts of preventive analgesia include initiating analgesia early, ensuring that the degree of analgesia is appropriate to address the severity of pain, and continuing analgesia until pain and inflammation has subsided.

Research in human patients has shown that preventive analgesia is the preferred approach for controlling acute post-operative pain and preventing the development of chronic post-operative pain. Since inflammatory mediators play a critical role in the development of pain by sensitizing nociceptors and sensitizing dorsal horn neurons, peri-operative administration of NSAIDs is routinely practiced in both human and veterinary medicine.

The following sections describe evidence to support use of Rimadyl for treatment of surgical pain, including an overview of Rimadyl pharmacology, efficacy, and safety.

RIMADYL PHARMACOLOGY

Carprofen, the active ingredient of Rimadyl, is a NSAID of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Rimadyl is eliminated primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites in the feces (70-80%) and urine (10-20%). Rimadyl also undergoes entero-hepatic recirculation to some extent. Since elimination involves both hepatic and renal components, caution is warranted when using Rimadyl in dogs with hepatic or renal dysfunction.

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Pharmacokinetics of Rimadyl Injectable

Pharmacokinetics describes the absorption, metabolism, distribution, and elimination of a drug (i.e., what the body does to a drug), and provides information for determining the dose and dosing schedule of a drug. While drug efficacy typically depends upon the achievement of therapeutic concentrations in targeted tissues or organs, plasma concentrations are often used to represent tissue concentrations and are noninvasive and easier to collect. In some cases, however, plasma pharmacokinetics may not accurately predict tissue concentrations (e.g., highly protein-bound drugs). Furthermore, when using pharmacokinetics to predict clinical outcome, these studies should be conducted in a manner consistent with conditions under which the drug is used in clinical practice.

A study conducted under ‘real-world’ clinical conditions evaluated the pharmacokinetics of Rimadyl Injectable when administered to anesthetized dogs undergoing ovariohysterectomy.40 Rimadyl Injectable was administered SC at 4 mg/kg* body weight, either prior to surgery or just after extubation. In addition, a control group of dogs received placebo treatments, to allow assessment of Rimadyl analgesic efficacy. Pharmacokinetic results summarized in Table 1 and Figure 4 reveal that the median time to maximum plasma concentration (T_max; can predict onset of activity) and the median drug half-life (t_1/2; can predict

*P < 0.05, Mann-Whitney statistical test

Table 1 – Carprofen pharmacokinetic outcomes following pre-operative or post-operative administration of Rimadyl Injectable (4.0 mg/kg SC) in dogs undergoing ovariohysterectomy.40

<table>
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<tr>
<th></th>
<th>T_max (hours)</th>
<th>C_max (µg/mL)</th>
<th>t_1/2 β (hours)</th>
<th>AUC_\text{last} (µg•hr/mL)</th>
<th>AUMC_\text{last} (µg•hr^2/mL)</th>
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<td>Statistical significance (pre vs post)</td>
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*The approved label dose for Rimadyl is 4.4 mg/kg/day in the US. Studies using a dose of 4.0 mg/kg reflect the approved label dose in Europe.
duration of effect) were similar for pre-operative (T_{max} 3.0 h; t_{1/2} 16.43 h) and post-operative (T_{max} 4.0 h; t_{1/2} 22.23 h) Rimadyl administration. These pharmacokinetic parameters correlate with outcomes of clinical studies which found that the analgesic effects were detected within 2 hours after administration, and the duration of analgesia to last up to 24 hours.\textsuperscript{40,46-50}

This pharmacokinetic study using anesthetized dogs also compared the analgesic efficacy of pre-operative vs post-operative administration of Rimadyl Injectable. Results summarized in Figure 5 indicate that pre-operative Rimadyl administration provided:

- significantly better analgesia at 2 hours post-operatively compared to post-operative Rimadyl administration;
- significantly better analgesia at 2, 4, and 8 hours post-operatively compared to the control group.

In contrast, post-operative Rimadyl administration only provided significantly better analgesia at 2 hours post-operatively vs the control group.

It is interesting that even though peak plasma concentrations (C_{max}) and the total drug exposure (area under the curve, or AUC) were significantly greater for dogs that received post-operative Rimadyl Injectable, a greater degree of analgesia was achieved with pre-operative administration. One reason for improved analgesia with pre-operative Rimadyl administration could simply be due to timing. Since the Rimadyl onset of activity is approximately 2 to 4 hours, the fact that pre-operative administration provided better post-operative analgesia is not surprising.

However, several other pharmacokinetic factors could also help explain why pre-operative administration of Rimadyl Injectable provided better post-operative analgesia. The researchers suggest that the lower median carprofen plasma concentration observed after pre-operative Rimadyl administration may be a reflection of higher tissue concentration, likely related to vasodilation caused by the anesthetic agents used in the study (acepromezine, thiopental, and halothane). Intra-operative vasodilation can increase the volume of distribution, which increases tissue exposure.
to Rimadyl and, therefore, increases tissue concentration.\textsuperscript{40} Limiting increased tissue concentration of Rimadyl to the surgical site would be desirable since this is the target for both the anti-inflammatory and analgesic effects. Because Rimadyl is highly protein bound (>99%), limited passage from the plasma to tissues occurs, with the exception of inflammatory exudates.\textsuperscript{51,52} Since the inflammatory response generated by surgical trauma causes plasma proteins to infiltrate and concentrate at the surgical site, Rimadyl concentration may also be increased at the surgical site due to binding to these proteins. Therefore, an increase in Rimadyl tissue concentration at the surgical site could be the result of: 1) the effects of anesthetic drugs on drug distribution; 2) the effects of inflammation on protein concentration at the surgical site; and 3) the high protein-binding capacity of Rimadyl; and may further explain why pre-operative administration can provide better post-operative analgesia.

A final consideration is the fact that up-regulation of COX-2 enzymes and release of prostaglandins occurs 2 to 8 hours after tissue injury.\textsuperscript{31} Pre-operative Rimadyl administration could allow therapeutic drug concentrations at the surgical site to coincide with COX-2 enzymes up-regulation and prostaglandin production. By inhibiting prostaglandin synthesis early in the inflammatory response, pre-operative administration of an NSAID can preemptively decrease the inflammation and pain associated with surgery.\textsuperscript{31} Together, these various factors help explain the differences in pharmacokinetics and analgesic effects associated with pre-operative vs post-operative administration of Rimadyl Injectable, and lend strong support for the administration of Rimadyl Injectable before surgery.

### Bioequivalence of Oral and SC Rimadyl

Another pharmacokinetics study investigated the bioequivalence of the oral and injectable Rimadyl formulations after administration of a single dose of approximately 2.2 mg/kg (1 mg/lb) in awake laboratory dogs.\textsuperscript{53} Pharmacokinetic values generated in the study (Table 2) differ from those reported in the previous study\textsuperscript{40} because a lower dose was evaluated (2.2 mg/kg vs 4.0 mg/kg) and the study was conducted in awake dogs (outcomes free of any impacts of anesthesia and surgery on the pharmacokinetics of pre-operative Rimadyl)

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<tr>
<th>Formulation</th>
<th>Pharmacokinetic parameters (±SD)</th>
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<tr>
<td></td>
<td>$T_{\text{max}}$ (hours)</td>
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<tr>
<td>Oral</td>
<td>1.05 (±0.76)</td>
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<tr>
<td>Injectable</td>
<td>2.58 (±1.64)</td>
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SD = standard deviation; AUC = area under the time concentration curve; $C_{\text{max}}$ = maximum plasma concentration; $T_{\text{max}}$ = time to maximum plasma concentration; $t_{\frac{1}{2}}$ = plasma half-life.
administration). In the bioequivalence study, similar total drug exposure calculated as the area under the curve (AUC) was generated by a single dose of either formulation of Rimadyl, although the peak plasma concentration (C\text{max}) was lower and the T\text{max} was longer for the injectable formulation. As seen in the previous study and several other clinical trials, C\text{max} and T\text{max} may not necessarily correlate with therapeutic effect.\textsuperscript{40,46,47,49,54} The researchers concluded that AUC was the parameter most relevant for assessing bioequivalence between the oral and injectable formulations.

The similar AUC values generated by oral and SC administration of Rimadyl indicated bioequivalence and suggested that the two formulations can be used interchangeably.\textsuperscript{46,53} This important finding confirmed that dogs treated pre-operatively with Rimadyl Injectable can experience continuity in analgesia when subsequently treated with the oral Rimadyl formulation.

**Efficacy of Rimadyl Injectable**

**Control of Post-Operative Pain and Inflammation**

Multiple studies have demonstrated the effectiveness of Rimadyl Injectable for controlling pain and inflammation associated with canine soft-tissue and orthopedic surgery. In 3 studies conducted to receive FDA approval for control of post-operative pain, Rimadyl Injectable was administered SC at 4.4 mg/kg approximately 2 hours prior to surgery, followed by 4.4 mg/kg SC once daily for 2 additional days for dogs undergoing soft-tissue surgery (ovariohysterectomy and aural surgeries), or 3 additional days for orthopedic surgery (cruciate repair).\textsuperscript{46} Responses were compared to placebo controls which received pre- and post-operative saline injections. Post-operative pain was evaluated at 4, 8, and 12 hours after surgery, and then twice daily until the end of the study. In all 3 studies, the Rimadyl-treated dogs experienced significantly better pain control than dogs in the placebo group. The dogs that received Rimadyl for aural surgeries had better pain control at 4, 8, and 12 hours post-surgery and at the first assessments on the day after surgery. Similarly, dogs that received Rimadyl for ovariohysterectomy experienced significantly better pain control at 4, 8, and 12 hours after surgery and at the first and second assessments on the day after surgery. Finally, the dogs that received Rimadyl for cruciate repair had significantly better pain control at all assessment periods through the third day post-surgery.

Other published studies have also investigated the efficacy of Rimadyl Injectable. As discussed previously in the Pharmacology section, a 1998 study found that administration of Rimadyl (4 mg/kg* SC) prior to surgery (ovariohysterectomy) provided significantly better pain control than the same dose administered post-operatively.\textsuperscript{40} Furthermore, administration of both pre-operative or post-operative Rimadyl treatment provided the best duration of analgesia and also reduced signs of peripheral and central sensitization. More recently, a 2012 study found that Rimadyl was effective in controlling post-operative pain for dogs undergoing tibial plateau leveling osteotomy (TPLO).\textsuperscript{55} The study compared dogs that received pre-operative Rimadyl (4 mg/kg SC) vs those that received a placebo control. Both groups were maintained on isoflurane and intra-operative constant-rate infusion of sufentanyl. Although intra-operative requirements for sufentanyl did not differ between groups, Rimadyl-treated dogs demonstrated superior cardiovascular stability (lower heart rate and mean arterial pressure), an observation thought to indicate better intra-operative analgesia compared to the controls. The Rimadyl Injectable group also had lower post-operative pain scores starting at 30 minutes after intubation (approximately 2 hours after administration of Rimadyl) and at most time points evaluated. A significantly lower incidence of dysphoria and lower dose requirement for buprenorphine (the rescue drug) was also reported for dogs treated with Rimadyl vs the control group. The researchers concluded that preemptive administration of Rimadyl Injectable contributed to improved quality of recovery, post-operative comfort, and analgesia.

\textsuperscript{*}The approved label dose for Rimadyl is 4.4 mg/kg/day in the US. Studies using a dose of 4.0 mg/kg reflect the approved label dose in Europe.
Rimadyl Injectable vs Opioids

Multiple studies have evaluated the efficacy of Rimadyl compared to opioids such as pethidine (meperidine), morphine, and buprenorphine. The first study compared the analgesic effect of Rimadyl vs pethidine in dogs undergoing orthopedic surgery. Dogs in the Rimadyl group received a single pre-operative dose at 4 mg/kg SC while dogs in the pethidine group received a 5.0 mg/kg SC dose before and after the procedure. Pain assessments were made at 1, 2, and 4 hours after surgery, later on the evening of surgery, and the day after surgery. Mean pain scores were significantly lower for Rimadyl-treated dogs at each time period compared to dogs treated with pethidine.

In another study, dogs undergoing ovariohysterectomy were treated pre-operatively with either: 1) Rimadyl (4 mg/kg SC); 2) pethidine (5.0 mg/kg SC); or 3) a combination of Rimadyl and pethidine (4 mg/kg SC and 5.0 mg/kg SC, respectively). Compared to dogs treated with pethidine alone, dogs in the Rimadyl and Rimadyl+pethidine groups had lower pain scores from 4 to 20 hours post-surgery (assessments ended at 20 hours post-surgery). Dogs in the pethidine group also required significantly more rescue analgesia than dogs treated with Rimadyl or with the Rimadyl+pethidine combination. Although the short duration of action for pethidine (approximately 2 hours) was likely the primary reason for the increased pain scores in pethidine-treated dogs, the researchers reported that the Rimadyl+pethidine group showed decreased signs of central sensitization compared to the other groups, indicating a possible additive or synergistic effect between Rimadyl and pethidine.

The analgesic effect of Rimadyl (4 mg/kg SC) was compared to buprenorphine (0.02 mg/kg IM) or the combination of both drugs administered pre-operatively to dogs undergoing ovariohysterectomy. Dogs treated with Rimadyl and Rimadyl+buprenorphine had superior pain scores compared to the dogs treated with buprenorphine alone. However, the combination of the two drugs did not improve pain control vs Rimadyl alone. Investigators in this study also evaluated the anti-inflammatory effects of Rimadyl by assessing wound swelling. At 2

hours and 8 hours after surgery, dogs treated with Rimadyl or the Rimadyl+buprenorphine combination demonstrated significantly less wound swelling than dogs treated with buprenorphine alone. Buprenorphine had a dose-sparing effect on the induction agent, whereas Rimadyl did not. Although the Rimadyl+buprenorphine combination did not provide additional analgesia in this study, the dose-sparing effects of buprenorphine on propofol induction, together with the analgesia and decreased wound swelling provided by Rimadyl, supports the use of Rimadyl and buprenorphine together as a multimodal peri-operative anesthesia/analgesia protocol.

A fourth study compared the post-operative analgesic effect of Rimadyl to that provided by morphine. Dogs undergoing ovariohysterectomy received either: 1) Rimadyl before surgery (4 mg/kg SC); 2) morphine before surgery (0.4 mg/kg SC, followed by morphine every 4-6 hours post-operatively); or 3) both Rimadyl and morphine (same dosages/ regimens). Dogs treated with Rimadyl experienced post-operative analgesia equivalent to the morphine group and the Rimadyl+morphine group at each time point (1, 2, 4, 6, and 20 hours post-surgery). Failure to show synergy between the two drugs was unexpected. The authors recommended additional studies to evaluate the synergistic effects of the two drugs.

Rimadyl has been shown to provide post-operative analgesia similar to morphine or superior to pethidine or buprenorphine when administered pre-operatively to dogs undergoing ovariohysterectomy. However, NSAIDs (i.e., Rimadyl) can provide additional benefits in a surgical setting.
• A single SC injection of Rimadyl delivers effective pain relief for up to 24 hours when administered at a dose of 4.4 mg/kg (2.0 mg/lb). In contrast, most opioids are short-acting and necessitate multiple administrations or constant rate infusions to deliver continuous analgesia over a 24-hour period.

• Rimadyl has been shown to provide anti-inflammatory effects, and decrease swelling at the surgical site.

• Rimadyl is not a DEA-controlled substance, so the extra recordkeeping steps required for scheduled drugs are eliminated.

Ultimately, the final decision on which drug or combination of drugs to use must be made on a case-by-case basis taking into consideration the physiological status of the patient and the degree of pain associated with the surgery.

Pre-Operative vs Post-Operative Rimadyl Injectable

As discussed, the inflammatory response to surgical trauma is initiated by COX-2 enzyme-mediated synthesis of prostaglandins. Increased synthesis of COX-2 enzymes occurs within 2 to 8 hours after trauma.31 When Rimadyl is administered 2 hours prior to surgery, the time required to reach therapeutic tissue levels coincides with the up-regulation of COX-2 enzymes; but if administered post-operatively, inhibition of inflammation and injury-related pain control is delayed.40,48 However, differences in analgesia between the 2 dosing strategies does not last through the entire post-operative period (no significant differences by 4 hours post-surgery). Therefore, the decision to administer injectable Rimadyl before surgery vs afterwards should be determined on a case-by-case basis. If Rimadyl Injectable is not used pre-operatively for control of post-operative pain, care should be taken to provide other analgesics to prevent or minimize initiation of peripheral and central sensitization.

Rimadyl Injectable for Dental Patients

Rimadyl is an excellent choice for controlling peri-operative pain associated with canine dental procedures because such pain is often related to inflammation involving the gingiva, periodontal ligament, and alveolar bone. Injectable Rimadyl is appropriate for most dental procedures in dogs, from comprehensive teeth cleaning to oral surgery.

Periodontitis is the most prevalent disease in companion animals.29 It is a condition caused by local infection from the bacteria in plaque, resulting in gingival inflammation and pain. When ignored, periodontitis can lead to destruction of the gingiva, periodontal ligament, and alveolar bone. Inflamed gingiva can bleed when touched with a probe or ultrasonic scaler. In such patients, it is assumed that manipulation of the inflamed tissue during a dental cleaning activates the nociceptive pathway (i.e., is painful). In cases of advanced periodontal disease, extraction of teeth may be necessary, and surgical removal will inevitably result in pain and swelling.

Rimadyl Injectable inhibits prostaglandins which are responsible for the primary inflammation and the pain associated with the inflammatory cascade. Even when teeth or tooth extractions are not performed, pre-operative administration of Rimadyl Injectable can offer great benefit. The injectable route of administration provides analgesia in the fasted anesthetic patient undergoing dental procedures, and a single SC Rimadyl injection provides 24 hours of analgesia. Eliminating the need for additional oral dosing for a full day eliminates both the need for client compliance during the immediate post-operative period as well as the administration of an oral medication to a dog that may be experiencing oral pain.

Dental procedures in dogs are performed under general anesthesia. A pre-anesthetic patient assessment (including physical exam, blood work, urine specific gravity, and other diagnostics) is essential in helping to choose the most appropriate drug regimen for pre-medication, induction, and post-operative analgesia. It is critical that the patient be well hydrated and normovolemic during surgery. Since many patients are fasted prior to surgery, judicious use of intravenous (IV) fluids should be a part of all anesthetic protocols.60,61 As with any anesthetic event, appropriate monitoring is essential and should include blood pressure monitoring throughout the procedure.
SAFETY OF RIMADYL INJECTABLE

Known NSAID Safety Profile

Although generally considered safe, all approved veterinary NSAIDs have the potential to cause side effects, regardless of their COX-1 and COX-2 selectivity or route of administration. As a class, NSAIDs have the potential for causing GI, renal, and hepatic side effects.

When discussing the safety profile of a drug, it is important to understand the difference between inducible and idiosyncratic reactions. Inducible adverse reactions are predictable, are associated with the drug’s mechanism of action, and are dose dependent (the frequency and severity of the adverse reaction increases with increased dosage). Inducible reactions are the most common type of adverse events.62 For NSAIDs, these include the potential for dysfunction of the kidneys and platelets, and disruption of GI tract integrity.

Idiosyncratic reactions are unpredictable, are not associated with the mechanism of action, and are not dose related. The underlying causes of idiosyncratic reactions are not well understood and may differ for each drug, each type of reaction, and each individual patient. Possible underlying causes include a hypersensitivity to the drug or an individual’s inability to appropriately metabolize the drug. Metabolic alterations can result in the development of toxic metabolites or inability to rapidly eliminate toxic metabolites. Idiosyncratic reactions are rare and typically occur early in the course of treatment,63 but can be severe and life threatening. For NSAIDs, hepatotoxicity is a potential idiosyncratic reaction.

Rimadyl Injectable Pharmacovigilance

Pharmacovigilance refers to the collection, assessment, reporting, detection, and prevention of drug reactions associated with a pharmaceutical product. Reports on drug reactions for companion animal medicines are submitted by veterinarians and pet owners. When reporting adverse events, frequency is often qualified by descriptive terms such as common, infrequent, and rare or very rare, as defined in Table 3.64 A summary of these reports involving Rimadyl Injectable from 2003 to 2013 is presented in Table 4 (data for 2003 represent a partial year, after approval of Rimadyl Injectable in March).65 Data for each year is presented by system or organ class, quantifying the total number of reports, and reports per 10,000 treated dogs (number of dogs treated calculated from market research data tracking dogs treated on an annual basis). A ‘case’ represents an adverse event for one animal while a ‘report’ represents a single symptom or clinical sign (multiple clinical signs or reports could be included in a single case). Thus, the number of reports is greater than the number of cases. The total annual number of cases is reported at the bottom of the column for each year.

All adverse-event reports submitted for Rimadyl Injectable are included in Table 4 regardless of causality. In other words, even if the circumstances under which the adverse event occurred indicated that some other cause was more likely than Rimadyl Injectable administration to result in the clinical signs (such as underlying disease or administration of another drug), the report was still included. Data in Table 4 indicate that adverse event reports for Rimadyl Injectable for a specific system or organ class were ‘rare’ or ‘very rare’, and that the reported rates have either remained constant or decreased over time.

The following discussion reviews the safety considerations and potential effects on different organ systems that have been reported for NSAIDs as a class, followed by a review of studies that evaluated the safety of Rimadyl in these organ systems.
Table 4 – Pharmacovigilance reports of drug reactions in dogs involving Rimadyl Injectable from 2003 to 2013.65

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a Death (includes euthanasia) as case outcome.
## Zoetis NSAID Technical Bulletin

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Renal Effects: COX Enzymes, Prostaglandins, and Renal Homeostasis

Regulation of renal homeostasis is complex with a number of checks and balances, including the production and function of prostaglandins. NSAIDs can affect renal function by inhibiting synthesis of renal prostaglandins, which are important for sodium and potassium homeostasis and for maintaining renal blood flow in the volume-depleted state.\(^66-69\) COX enzymes are constitutively expressed in the kidneys. In the dog, COX-1 is found predominantly in the collecting tubules and renal vasculature, and COX-2 in the macula densa, medullary interstitial cells, and the thick ascending limb.\(^70\) COX enzymes regulate sodium and water absorption through PGE\(_2\) production and potassium levels through PGI\(_2\) production.\(^71\) COX inhibition has little effect on electrolyte homeostasis in the normovolemic dog. Under normal conditions, prostaglandins have little influence on renal blood flow (RBF) or glomerular filtration rate (GFR). However, if renal blood flow is impaired due to hypotension or hypovolemia, COX-2 enzymes are up-regulated and synthesis of PGI\(_2\) and PGE\(_2\) increases in response to vasoconstriction of the renal artery.\(^6,7,70\) Under volume-contracted states, increased levels of catecholamines, angiotensin, and vasopressin contract renal arteries. Prostaglandins counteract the vasoconstrictive effects of these hormones, preserving RBF and GFR.\(^8\) Therefore, use of COX-2 inhibitors should have little effect on renal blood flow or electrolyte balance in the normovolemic or normotensive patient, but may prevent the cytoprotective effects that the COX-2-derived prostaglandins provide in maintaining renal perfusion and GFR in the hypovolemic or hypotensive patient.

Renal Safety of Rimadyl Injectable

Zoetis pharmacovigilance found the reporting rate for renal adverse events to be very rare. Four separate studies found that pre-operative administration of Rimadyl Injectable in normovolemic and normotensive dogs resulted in no significant difference, compared to placebo-controlled groups, on various renal parameters including GFR, serum blood urea nitrogen (BUN), serum creatinine, urine protein, urine creatinine, or the ratio of urine \(\gamma\)-glutamyltransferase (GGT) to urine creatinine (urine GGT: creatinine).\(^72-75\) Another study evaluated the effects of pre- or post-operative administration of Rimadyl Injectable (4 mg/kg, IV*) on renal function in dogs with low blood pressure (mean arterial pressure maintained at 65 mm Hg).\(^76\) No significant differences in hematological, serum biochemical, urinalysis, angiotensin II and arginine-vasopressin values, or GFR (measured with scintigraphy) were detected compared to placebo (saline) controls.

A research team evaluated creatinine clearance (CC) in dogs 24 hours after undergoing castration.\(^77\) Mean CC was significantly lower \((P < 0.01)\) for dogs treated with Rimadyl (4 mg/kg, SC) or with ketoprofen (2 mg/kg, SC) compared to control animals (CC values: 2.29 ± 0.17 mL/kg/m; 2.07 ± 0.45 mL/kg/m; 3.12 ± 0.85 mL/kg/m, respectively). Although mean CC values for the Rimadyl and ketoprofen groups were lower than that of control dogs, values were within the normal range (2.5 mL/kg/m) for non-anesthetized dogs and similar to another study evaluating GFR using CC in anesthetized dogs.\(^75\) No differences between the Rimadyl and ketoprofen groups were detected. Confounding factors in this study included the lack of baseline measurements, use of two anesthetic agents known to cause hypotension (acepromazine and thiopentone), and no peri-operative administration of IV fluids or monitoring of blood pressure. Although all treated dogs had CC values within normal limits, the researchers concluded that pre-operative use of NSAIDs should be undertaken with care.

A renal function study evaluated 40 dogs (10 dogs/group) treated with either Rimadyl (4.0 mg/kg SC), ketoprofen (1.0 mg/kg SC), or ketorolac (0.5 mg/kg SC) compared to a morphine control group (0.1 mg/kg SC).\(^78\) Renal function was assessed using urine specific gravity (USG), creatinine, BUN, fractional clearance of sodium (FC\(_{\text{Na}}\)), and urine enzymes including urine GGT, urine GGT:creatinine ratio, urine alkaline phosphatase (ALP), and urine ALP:creatinine ratio. No differences were observed in urine enzymes or urine ALP: creatinine ratio. Transient azotemia was reported in 2 dogs in each of the ketorolac and ketoprofen groups. The azotemia persisted through 48 hours after anesthesia in both ketorolac-treated dogs and 1 ketoprofen-treated dog. Renal tubular epithelial cells were

*US approval of Rimadyl Injectable is at 4.4 mg/kg/day administered as SC injection. Studies using a dose of 4.0 mg/kg reflect the approved label dose in Europe.
found in urinalysis of 4 dogs from the morphine group, 2 dogs from the ketorolac group, and 1 dog each from the Rimadyl and ketoprofen groups. In this study, FC_{Na} >1 was used as an indicator of acute tubular dysfunction. FC_{Na} >1 was reported in 4 ketorolac-, 5 ketoprofen-, and 2 Rimadyl-treated dogs at 24 hours, but decreased to <1 by 48 hours. However, since FC_{Na} >1 was reported for several dogs at the pre-surgical assessment, the authors questioned the sensitivity of FC_{Na} >1 as an indicator of acute tubular dysfunction and attributed the change in FC_{Na} over the 24- to 48-hour post-surgery period to factors related to anesthesia and independent of renal dysfunction. They concluded that peri-operative use of NSAIDs was not contraindicated and that Rimadyl had the least effect on renal function and integrity.

Two separate studies evaluated the effects of oral Rimadyl, ibuprofen, or etodolac on renal function alone or in combination with furosemide. Furosemide administration was used as a model representing volume-depleted dogs. The studies employed a randomized cross-over design and measured parameters included USG, BUN, creatinine, electrolytes, GFR, and renal plasma blood flow (RBF) prior to treatment and after 8 days of treatment. A wash-out period of 10 to 13 days was allowed between treatments. Results showed that administration of Rimadyl, ibuprofen, or etodolac, alone, did not have a significant effect on any of the parameters. Dogs treated with furosemide alone had significantly lower USG and significantly higher BUN and creatinine compared to placebo control, but the GFR and RBF were not significantly different. However, combination treatment involving furosemide plus any of the NSAIDs significantly lowered USG and GFR and significantly increased BUN and creatinine compared to placebo controls or NSAIDs alone. Additionally, GFR values for dogs treated with furosemide+Rimadyl or furosemide+ibuprofen were significantly lower than dogs treated with furosemide alone. These reductions of GFR were considered mild because they did not result in azotemia or illness. After drug withdrawal, all parameters returned to pre-treatment values for all groups. This study showed that transient changes in renal function occur when NSAIDs are administered concurrently with diuretics, and confirms prior precautions regarding the concurrent use of these two classes of drugs. These studies also suggest that use of NSAIDs in volume-depleted dogs can have transient effects on the kidneys, and supports previous precautions regarding NSAID use in these situations.

In summary, NSAIDs have little effect on renal perfusion in healthy dogs, but may interfere with the autoregulatory function of prostaglandins, which becomes important during hypotension or hypovolemia. Inhibition of COX-2 enzymes and prostaglandins may interfere with the body’s ability to compensate for reductions in renal blood flow, potentially leading to kidney damage. Studies evaluating the effects of pre-operative Rimadyl administration have found no clinically relevant effects in healthy dogs that are normotensive or have low blood pressure. Transient renal effects were identified in dogs that were artificially ‘volume depleted’ from 8 days of concurrent administration with furosemide, but all parameters returned to normal after drug withdrawal.

Pre-operative use of NSAIDs for control of post-operative pain is appropriate in normal, healthy patients. The benefits of using Rimadyl Injectable pre-operatively to control post-operative pain and inflammation have been documented in numerous studies. However, as with any surgical procedure, patients should be monitored and attention should be focused on keeping the patient hydrated, normotensive, and normovolemic. Since many anesthetic drugs (e.g., acepromazine, propofol, gas inhalants) can cause hypotension and hypothermia, blood pressure, heart rate, body temperature, etc., should be monitored throughout the entire anesthetic event, including recovery, so that appropriate and timely adjustments can be made if a patient’s status changes.

Patients at risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or have renal, cardiovascular, or hepatic dysfunction. NSAID therapy should be avoided in dogs with decreased renal perfusion due to shock, dehydration, and hemorrhage. If intra-operative hypotension or hypovolemia is a concern, then NSAID administration can be postponed until cardiovascular homeostasis has been restored.
Platelet Effects: COX Enzymes, Prostaglandins, and Hemostasis

The use of NSAIDs before surgery is sometimes discouraged because some drugs in this class, such as aspirin, have been associated with increased peri-operative bleeding. Platelet function is regulated by thromboxane (causes vasoconstriction and platelet aggregation) and prostacyclin (acts as a vasodilator and an anti-coagulant). Thromboxane synthesis from platelets is induced by COX-1. COX-1 inhibition causes irreversible inhibition of thromboxane synthesis since platelets lack a nucleus and are unable to synthesize additional COX-1 enzymes or thromboxane. Therefore, the only way to synthesize additional thromboxane after COX-1 inhibition is through the generation of new platelets. In contrast, prostacyclin synthesis from endothelial cells is induced by COX-2 enzymes, and is reversible since endothelial cells are capable of synthesizing additional prostacyclin. Since COX-1 and COX-2 enzymes are involved in the maintenance of hemostasis, use of NSAIDs can interfere with hemostasis.

NSAIDs that indiscriminately inhibit both COX-1 and COX-2 (such as aspirin) increase the risk of bleeding, because the net effect of these drugs is to irreversibly inhibit thromboxane but not prostacyclin, thereby shifting the hemostatic balance away from coagulation. Alternatively, COX-1-sparing drugs inhibit prostacyclin to a greater degree than thromboxane. These drugs have the potential to increase the risk of developing thrombosis because the hemostatic balance has shifted toward coagulation. Increased incidence of myocardial infarction has been reported in human medicine, especially with drugs highly selective for COX-2 enzyme. In fact, patients that received Vioxx® (rofecoxib), a COX-2-selective NSAID, experienced an increased incidence of myocardial infarction, prompting the FDA to withdraw the drug from the market in 2004. In human medicine, myocardial infarctions are typically associated with atherosclerosis. However, the incidence of atherosclerosis in dogs is very rare because metabolism of fats does not result in low-density lipoproteins and cholesterol formation, so dogs are not predisposed to myocardial infarctions. Increased risk of thrombosis associated with COX-1-sparing drugs has not been reported in veterinary medicine and is likely related to the fact that dogs are not predisposed to development of myocardial infarctions.

Platelet Safety of Rimadyl Injectable

The effects of Rimadyl Injectable on coagulation were evaluated in studies submitted to the FDA to support the indication for control of post-operative pain and inflammation. No significant differences were noted in the coagulation parameters of dogs treated with Rimadyl (4.4 mg/kg SC) 2 hours before surgery compared to placebo control dogs. Zoetis pharmacovigilance data show the rate of reported blood abnormalities to be rare to very rare.

Additional studies were conducted after approval of Rimadyl Injectable. One study evaluated the hemostatic effects of Rimadyl Injectable administered SC at 4 mg/kg 1 hour before orthopedic surgery, or just after extubation, followed with oral Rimadyl (4 mg/kg) once daily for 4 days. Hemostatic variables measured in the study included prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count, bleeding time, and platelet aggregation. Most hemostatic values did not significantly differ between the 2 groups. Bleeding times were within reference range for all animals at all time points during the study. However, PT, APTT, and platelet aggregation values were outside reference ranges for many dogs before surgery and before Rimadyl administration. These changes were considered to be trauma-induced and were not clinically significant at any time during the study. Most values returned to normal during the 4-day post-operative period. The authors concluded that administration of Rimadyl Injectable did not have any clinically relevant effects on hemostasis in dogs anesthetized for fracture repair, even when administered to dogs that had trauma-induced alterations in hemostasis.

Other studies evaluating the short-term effects of Rimadyl oral formulation on hemostasis have shown variable results. One report determined that oral Rimadyl administration at 4.4 mg/kg once daily for 7 days did not significantly affect platelet function, platelet aggregation, PT, APTT, or fibrinogen when compared to baseline. Other studies evaluated the hemostatic effects of several NSAIDs, including Rimadyl given 2.2 mg/kg PO twice daily; Rimadyl given at 4.0 or 4.4 mg/kg PO once daily; meloxicam given 0.2 mg/kg PO on day 1 followed by 0.1 mg/kg PO once daily; or deracoxib 2 mg/kg PO once daily. Dogs received each treatment for 5-7 days in a crossover design with an appropriate

*The approved label dose for Rimadyl is 4.4 mg/kg/day in the US.
Studies using a dose of 4.0 mg/kg reflect the approved label dose in Europe.
wash-out period between treatments. Although variable results were seen in platelet function across treatments, no differences in bleeding times were noted. The overall conclusion from these studies is that NSAIDs may affect in vitro measurements of platelet function. However, these in vitro assessments were not associated with clinically relevant changes.

In summary, studies evaluating hemostatic effects of injectable or oral Rimadyl formulations for up to 7 days did not find any clinically relevant impacts on platelet function or coagulation. However, since all NSAIDs exert some degree of COX-1 inhibition, platelet function and coagulation parameters should be assessed in advance of peri-operative NSAID use whenever risk factors for bleeding are present. Use of NSAIDs in dogs with known platelet deficiencies or coagulation defects is not recommended.1,89-91

Gastrointestinal (GI) Effects: COX Enzymes and GI Integrity

Potential GI toxicity is a consideration when any NSAID is used, whether peri-operatively or for chronic pain (such as osteoarthritis). The gastro-protectant effects of COX enzymes are due to PGE2 and PGI2 synthesis via several mechanisms including:92

- reduction of gastric acid production;
- increase of gastric blood-flow due to vasodilation;
- increase of mucous production and bicarbonate secretion.

COX-1-induced prostaglandins are maintained in healthy GI mucosa,93 but in inflamed and ulcerated GI mucosa, COX-1 production decreases and COX-2-induced prostaglandins become responsible for maintaining GI homeostasis.94,95 Although COX-1-sparing NSAIDs provide a better GI safety profile than non-selective NSAIDs (such as aspirin),96 COX-2-selective drugs may delay healing when the gastric mucosa integrity is compromised. These data indicate that both COX-1 and COX-2 are important for production of prostaglandins involved with ulcer healing.97

GI Safety of Rimadyl Injectable

Rimadyl is considered to be COX-1 sparing, and the importance of a canine-approved, COX-1-sparing NSAID was illustrated in a study where dogs received Rimadyl, etodolac, or aspirin followed by endoscopic and histopathological evaluation of the gastric and duodenal mucosa.97 All dogs treated with buffered aspirin had significantly greater gastric erosions and sub-mucosal hemorrhagic lesions compared to the other groups. Only minor lesions of the gastric mucosa were observed in dogs treated with Rimadyl or etodolac, and these changes were similar to changes noted in the placebo control group.

A recent in vitro study found that Rimadyl and meloxicam increased gastric permeability and appeared to compromise gastric mucosal barrier integrity and barrier function at the doses administered.98 However, the clinical relevance of this study is questionable since an in vivo study found that neither drug affected gastric permeability.99 Furthermore, in a clinical study that evaluated adverse effects of long-term use of a number of NSAIDs, drugs that were more COX-1 sparing (such as Rimadyl and meloxicam) generated fewer adverse effects than drugs with greater inhibitory effects on COX-1 (including etodolac, flunixin meglamine, and ketoprofen).100 Other studies comparing GI effects of various FDA-approved canine NSAIDs found no significant impacts on clinical outcomes (based on GI endoscopic and histopathological evaluation).101-103

Direct irritation of the GI mucosa is a potential effect of orally administered NSAIDs when gastric emptying is delayed.2 A study in human patients showed that IV aspirin caused no GI bleeding, but oral administration of unbuffered aspirin at the same dose and for the same duration caused substantial GI bleeding.104 A similar study, comparing the GI effects of oral vs injectable Rimadyl formulations, has not been conducted in canine surgical patients. Although orally administered canine NSAIDs approved for control of post-operative pain and inflammation have been demonstrated to be safe and effective, an injectable formulation may offer a better option in some dogs where a delay in gastric emptying is known or suspected. Delayed gastric motility could either delay absorption and onset of action, or increase topical exposure of the orally administered NSAID. Delayed gastric emptying can be caused by outflow obstruction (such as gastric polyps or tumors), foreign bodies, ileus, or pyloric stenosis. Defects in gastric motility due to stress, trauma, or surgery can also delay gastric emptying.
When using an injectable NSAID for controlling post-operative pain and inflammation, then continuing to an oral NSAID, it is recommended to avoid switching NSAIDs. Although one study found that Rimadyl Injectable followed by either 4 days of oral Rimadyl or deracoxib did not induce clinically relevant GI lesions, this was a laboratory study conducted in 6 conditioned dogs that did not undergo an anesthetic/surgical event, so the study did not properly represent possible risk associated with combined use in a peri-operative setting. In order to minimize possible GI effects, most experts recommend continuing with the same injectable and oral NSAID peri-operatively.

Though NSAIDs are well tolerated in the vast majority of dogs, GI signs are the most common adverse events associated with this class of drugs. In clinical studies, the frequency of GI adverse effects following a single peri-operative injection of Rimadyl was low, comparable to the incidence rate in placebo controls. Zoetis pharmacovigilance data collected since 1999 indicate that the annual rate of reported GI signs are rare to very rare. Since many dogs continue post-operative treatment with oral Rimadyl for several days or longer following the peri-operative injection, clients should be advised of the potential for GI side-effects and monitor their dogs accordingly. Reported clinical signs associated with GI adverse events include depression, anorexia, reduced appetite, vomiting, diarrhea, hematochezia, melena, and gastric ulceration. These clinical manifestations should be discussed with dog owners whenever oral NSAIDs are prescribed. Additionally, owners should be instructed to discontinue administration of the NSAID and call the veterinarian should their dog exhibit any of these clinical signs. An Owner Information Sheet (Attachment 1) provides important information on Rimadyl and is a useful tool for client education. Owner information sheets are available for all veterinary approved NSAIDs and should be given to all owners when their dogs receive a drug from this class.

Proper patient selection is important, including avoiding use of NSAIDs in dogs with a history of NSAID intolerance, pre-existing GI disease, or renal or hepatic dysfunction. NSAIDs should not be administered concurrently with glucocorticoids or other NSAIDs, and the veterinarian should be aware of all concurrently administered medications, including OTC agents, aspirin, and topical medications that contain glucocorticoids. When administering NSAIDs on a long-term basis and the need arises to switch from one NSAID to another, an appropriate wash-out period is strongly recommended. Recommendations for wash-out periods are based on the pharmacological properties of the drugs, but have not been confirmed in studies. However, based on the premise that the majority of the drugs are eliminated within 4 to 5 half-lives, a wash-out period of 5 to 7 days is typically recommended for most approved canine NSAIDs. A longer wash-out period of 7 to 14 days is recommended for aspirin due to the extensive COX-1 inhibition associated with this drug.

Bone Healing: COX Enzymes, Prostaglandins, and Bone Repair

The effects of COX-2 enzymes on bone healing were first identified in studies involving genetically engineered mice that were completely deficient in COX-2 enzyme and exhibited delayed bone resorption and bone healing. The role of COX-2 enzymes in bone metabolism was defined as a result of these and other experimental studies. In healthy bones, prostaglandin synthesis mediated by COX-2 enzymes maintains the pre-osteoblast population of cells. After bone injury, COX-2 enzymes are induced and stimulate osteoblast differentiation and proliferation through up-regulation of PGE2 production. A study in rats showed that COX-1 concentration at the fracture site remains low, while COX-2 expression significantly increases from day 3-14 and returns to baseline levels by day 21. Additional research confirmed that inflammation and early induction of COX-2 was crucial for bone healing, and that elimination of COX-2 at the early stage of healing could lead to detrimental effects on cortical bone repair. It is now accepted, based on the evidence, that for mammalian species the inflammatory response is essential for normal bone repair after injury, and COX-2 enzymes, along with a number of growth factors, play a role in bone healing.

In human clinical medicine, the use of NSAIDs for pain management immediately after orthopedic surgery has been questioned by some based on laboratory animal and in vitro studies. In most of these studies, delayed bone healing was associated with NSAIDs that were administered at super-therapeutic doses and/or for a prolonged period of time. Therefore,
the clinical relevance of these studies is questionable and the conclusions cannot be extrapolated to practical situations where therapeutic doses are administered for the appropriate period of time.

More recent laboratory studies in rats evaluated the effects of NSAID treatment duration on bone healing. Results indicated that short-term treatment (14 days) with either non-selective or selective COX-2 inhibitors had no effect on bone healing. Longer-term use of 21 days did delay bone healing, but these effects resolved within 14 days after cessation of the NSAIDs. Duration of treatment was also shown to affect bone growth in rabbits, where 2 weeks of treatment with NSAIDs did not affect bone growth but 6 weeks of treatment resulted in delayed growth.

Recent human clinical studies have found no correlation between NSAID use and occurrence of non-unions after surgical repair of fractures. A large-cohort study evaluating the role of NSAIDs in non-union of humeral shaft fractures found that neither NSAIDs nor opioids were associated with non-unions when administered for up to 60 days following surgery. However, a significant association with non-unions was observed when either NSAIDs or opioids were taken for 61 to 90 days. The authors concluded that the association of non-unions with longer-term use of NSAIDs or opioids was less likely due to long-term NSAID or opioid effect on bone healing but more likely a result of a prolonged need for analgesia by patients with painful non-healing fractures. A more recent 2010 meta-analysis of human clinical studies evaluating the effects of NSAIDs on bone healing found that NSAID use was not associated with an increased risk of non-unions in patients with fractures, osteotomies, or fusions.

**Rimadyl and Bone Healing**

Similar large-cohort studies or meta-analyses have not been conducted to assess the effects of NSAIDs on bone healing in dogs. However, the effects of Rimadyl on bone healing was evaluated in a laboratory study where a mid-diaphyseal transverse tibial osteotomy was repaired with an intramedullary pin. Rimadyl was administered to 6 of the dogs (2.2 mg/kg q 12 hours for 120 days) and results were compared to 6 control dogs. Results showed evidence of delayed healing in the Rimadyl group compared to the control group. However, study design factors limited extrapolation of results from this laboratory study to clinical situations. First, the method of fixation included placement of an intramedullary pin without providing rotational stability, a method that would not be acceptable in the clinical situation. A study conducted in rats showed that NSAIDs did not affect bone healing in stable fractures but did delay healing in unstable femoral fractures. Furthermore, 120 days of treatment for a traumatic fracture is longer than typically practiced. The healing effects of a shorter, more appropriate course of Rimadyl treatment were not evaluated. In contrast, other studies confirmed that if NSAID-associated delay in bone healing was observed, these changes resolved quickly after discontinuation of therapy. The authors did not conclude that NSAIDs were an inappropriate analgesic choice in orthopedic surgeries, but did recommended caution when treating fractures that have delays in healing or in dogs with diseases that predispose animals to delays in bone healing.

Clinical studies evaluating the effects of short-term or long-term treatment with NSAIDs on canine traumatic fracture repair have not been conducted. Judicious use of NSAIDs after fracture repair is common practice in veterinary patients, and is recommended for several days after treatment for bone fractures or other orthopedic surgery. It should also be noted that although the use of NSAIDs to control post-operative pain associated with fractures is a common practice, the rate of non-union fractures reported for dogs is 3.4%, and factors that influence non-union after fracture repair include location of fracture, (radial and ulna fracture), inadequate immobilization, inadequate reduction, impairment of blood flow due to trauma (original or surgical), infection, and loss of bone or bone fragments. Other general factors such as age, high-dose corticosteroid therapy, or metabolic alteration of osteoblastic activity may also affect the rate of bone healing but are uncommon factors contributing to delayed union or non-union fractures. The benefits of NSAIDs to provide analgesia and thus achieve earlier mobilization, weight bearing, and return to function should be weighed against the risk of delayed bone healing. Evidence supports use of NSAIDs for control of post-operative pain after orthopedic surgeries, providing the drugs are administered at therapeutic doses and for appropriate treatment durations to control pain and there are no predisposing factors that would
contribute to delayed healing. Determination of treatment duration should be based on the need for analgesia, the response to treatment, and the progress of bone healing.

**Hepatic Effects of NSAIDs**

As mentioned earlier, hepatotoxicity associated with drug administration is typically an idiosyncratic reaction. No study has reported hepatotoxicity associated with peri-operative administration of Rimadyl, and hepatobiliary adverse reactions reported for Rimadyl Injectable are very rare (<1/10,000 cases). A 1998 report documented 21 cases of hepatotoxicity associated with oral Rimadyl administration to dogs with osteoarthritis. Most signs of hepatotoxicity occurred within the first 30 days of treatment, and 17 of the 21 dogs responded to treatment. Other researchers evaluated 905 dogs with osteoarthritis that were treated with Rimadyl for 84 days. Two dogs demonstrated signs consistent with hepatotoxicity, and both dogs recovered within a few days after Rimadyl was discontinued and appropriate medical treatment was provided. Another study evaluated 71 dogs that received a glucosamine/ chondroitin nutraceutical, meloxicam, Rimadyl, or placebo for 60 days. One dog in the Rimadyl group developed hepatotoxicity and recovered with treatment. Several other studies evaluating long-term Rimadyl treatment (60, 90, or 120 days) in dogs with osteoarthritis did not detect any evidence of hepatotoxicity. Idiosyncratic hepatotoxicity is not unique to Rimadyl as this condition has also been reported for the other canine NSAIDs.

Labrador Retrievers were the most commonly reported breed to show hepatotoxicity in the 1998 report. The study did not differentiate for breed prevalence within the hospital population, and the increased numbers of Labrador Retrievers in this study were most likely due to both the popularity of Labrador Retrievers and high occurrence of osteoarthritis and other musculoskeletal conditions in this breed. No evidence exists to indicate that Labrador Retrievers are more susceptible to idiopathic hepatotoxicity associated with NSAIDs. However, Labrador Retrievers and several other breeds (e.g., Bedlington Terriers, Skye Terriers, Doberman Pinchers, and Dalmatians) are predisposed to copper-associated chronic hepatitis (CACH) which can affect dogs of various ages and is often asymptomatic. Elevations of ALP or alanine amino transferase (ALT) enzymes during routine blood work (with a greater relative increase in ALT vs ALP) is often the first evidence of CACH. Diagnosis is confirmed by identifying histopathological changes consistent with chronic hepatitis and elevated hepatic copper levels of liver biopsies. Initial screening and routine monitoring of blood work is recommended pre-operatively and additional diagnostics pursued when warranted. Although peri-operative use of Rimadyl Injectable is not expected to increase the risk of hepatotoxicity in dogs, pre-existing conditions need to be evaluated and considered when choosing peri-operative analgesics.

**DOSING FLEXIBILITY AND CONTINUITY OF ANALGESIA**

Rimadyl is the only NSAID available in both injectable and oral formulations where both are indicated for controlling post-operative pain and inflammation associated with soft-tissue and orthopedic surgeries for dogs, and is backed by over 10 years of research. Rimadyl is the only canine NSAID approved for use in puppies as young as 6 weeks of age. Both formulations can be administered as a single daily dose of 4.4 mg/kg (2.0 mg/lb) or divided into twice-daily doses at 2.2 mg/kg (1.0 mg/lb).

Rimadyl Injectable is labeled for administration via SC injection, a convenient method of administration that does not require IV access. The pharmacokinetic profiles of the oral and injectable formulations of Rimadyl are similar and total drug exposure is considered bio-equivalent, so both dosage forms can be used interchangeably. The availability of Rimadyl in both an injectable and oral form allows veterinarians to offer continuity of analgesia by using the same medication throughout the entire peri-operative period. Pre-operative use of Rimadyl Injectable at 4.4 mg/kg provides 24 hours of pain management. The oral formulation, either caplet or chewable tablet, can be used to continue post-operative pain management once the patient returns home. Also, with the trend to perform spays and neuters on very young puppies, Rimadyl provides veterinary practitioners a suitable option for providing pain relief in dogs as young as 6 weeks of age.

Although the oral and injectable forms of Rimadyl are approved for pre-operative administration for control of post-operative pain, use of the injectable formulation may provide some additional benefits. Many anesthetic pre-medications can cause vomiting and could potentially result in elimination of an orally administered drug prior to its complete absorption. Also, the stress experienced during the peri-operative period and the effect of anesthetic drugs on GI motility may interfere with normal absorption of the NSAID, resulting in suboptimal post-operative analgesia. Additionally, injury to the gastric mucosa can be initiated topically if there is delay in gastric emptying. Using Rimadyl Injectable pre-operatively eliminates variations in absorption of orally administered drugs that may occur during the peri-operative period and provides a predictable level of pain management during and after the procedure, for up to 24 hours.
CONCLUSIONS

NSAIDs are a mainstay of peri-operative pain management in canine surgery. Because inflammation is a key driver in the development of surgical pain, the anti-inflammatory activity of NSAIDs make this class of drugs a good choice for post-operative analgesia. Clinical and pharmacokinetic studies support the benefits of administering Rimadyl Injectable pre-operatively to control post-operative pain in dogs, as dogs that received Rimadyl prior to surgery had better immediate post-operative analgesia than dogs that received Rimadyl after surgery. Reasons for improved pain management with pre-operative administration vs post-operative administration can be attributed to many factors including:

1) the pharmacokinetic properties of Rimadyl;
2) the effects of anesthetic drugs on tissue concentrations;
3) use of preemptive analgesia.

Preemptive pain management, followed by appropriate intra-operative and post-operative analgesia, can circumvent central sensitization and prevent the onset of chronic, intractable pain. Rimadyl Injectable not only provides analgesia but also decreases swelling at the surgical site, another advantage of the anti-inflammatory effects of this drug which is not provided by other classes of analgesics.

The mechanism of action that allows NSAIDs to provide effective analgesia may also be responsible for adverse reactions in some patients. FDA-approved canine NSAIDs offer a better safety profile than aspirin and other non-veterinary NSAIDs. An individual patient’s risk of experiencing an adverse reaction to any of the approved canine NSAIDs depends on their medical status and tolerance for a specific NSAID. Timing of Rimadyl Injectable administration should take into consideration the individual patient’s health status. If there is a concern regarding renal perfusion or hemostasis before or during surgery, another class of analgesic drugs should be considered. However, in stable canine patients, the benefits of administering Rimadyl Injectable pre-operatively outweigh the risks and will provide up to 24 hours of analgesia.

Patient selection is also key for ensuring that NSAID benefits outweigh the risk of adverse effects. The use of NSAIDs should be avoided in patients with underlying liver, kidney, or GI disease. Also avoid concurrent use of NSAIDs with corticosteroids, including oral, topical, or injectable formulations, or other NSAIDs. Since most NSAID-associated adverse events are inducible, higher rates of adverse events can be seen with overdosing. Although Rimadyl has a wide margin of safety (up to 5× the dose for 1 year in laboratory studies), prudence dictates that Rimadyl be administered only at the approved label dose of 4.4 mg/kg/day. Pet owners should be instructed to securely store prescribed oral NSAIDs in an area inaccessible to the pet, to prevent accidental over-ingestion. In all cases, pet owners should be made aware of all potential risks associated with this class of drugs. They should also be counseled to recognize clinical signs associated with NSAID toxicity, and should be advised to discontinue NSAID administration and seek veterinary advice if these signs should occur. Whenever Rimadyl is dispensed, the pet owner should always receive a Client Information Sheet (see following page).

IMPORTANT SAFETY INFORMATION: As a class, NSAIDs may be associated with gastrointestinal, kidney, and liver side effects. These are usually mild, but may be serious. Pet owners should discontinue therapy and contact their veterinarian immediately if side effects occur. Evaluation for pre-existing conditions and regular monitoring are recommended for pets on any medication, including RIMADYL. Use with other NSAIDs or corticosteroids should be avoided. See full Prescribing Information, attached.
Dog Owner Information about RIMADYL® Caplets/Chewable Tablets

Rimadyl® (pronounced “Rim-a-dill”) for Osteoarthritis and Post-Surgical Pain. Generic name: carprofen (“car-prō-fen”)

Tell your veterinarian if your dog is:
- Pregnant, nursing or if you plan to breed your dog.

What are the possible side effects that may occur in my dog during Rimadyl® therapy?
Rimadyl, like other drugs, may cause some side effects. Serious but rare side effects have been reported in dogs taking NSAIDs, including Rimadyl. Serious side effects can occur with or without warning and in rare situations result in death.

The most common NSAID-related side effects generally involve the stomach (such as bleeding ulcers). Kidneys and liver can also be affected. Look for the following side effects that can indicate your dog may be having a problem with Rimadyl or may have another medical problem:
- Decrease or increase in appetite
- Vomiting
- Change in bowel movements (such as diarrhea, or black, tarry or bloody stools)
- Change in behavior (such as decreased or increased activity level, incoordination, seizure or aggression)
- Yellowing of gums, skin, or whites of the eyes (jaundice)
- Change in drinking habits (frequency, amount consumed)
- Change in urination habits (frequency, color or smell)
- Change in skin (redness, scabs or scratching)

It is important to stop therapy and contact your veterinarian immediately if you think your dog has a medical problem or side effect from Rimadyl therapy. If you have additional questions about possible side effects, talk to your veterinarian.

Can Rimadyl® be given with other medicines?
Rimadyl® should not be given with other NSAIDs (for example, aspirin, etodolac or steroids (for example, cortisone, prednisone, dexamethasone, triamcinolone).

Tell your veterinarian about all medicines you have given your dog in the past, and any medicines that you are planning to give with Rimadyl. This should include other medicines that can get without a prescription. Your veterinarian may want to check that all of your dog’s medicines can be given together.

What do I do in case my dog eats more than the prescribed amount of Rimadyl®?
Contact your veterinarian immediately if your dog eats more than the prescribed amount of Rimadyl.

How to store Rimadyl Chewable Tablets.
Rimadyl Chewable Tablets are designed to taste good to animals. Keep Rimadyl Chewable Tablets in a secured storage area out of the reach of your dog and other pets. If your dog ingests more than your veterinarian prescribed, or if your other pets take Rimadyl Chewable Tablets, contact your veterinarian right away.

What else should I know about Rimadyl®?
This sheet provides a summary of information about Rimadyl. If you have any questions or concerns about Rimadyl or osteoarthritis or surgical pain, talk to your veterinarian. As with all prescribed medicines, Rimadyl® should only be given to the dog for which it was prescribed. It should be given to your dog only for the condition for which it was prescribed.

It is important to periodically discuss your dog’s response to Rimadyl at regular checkups. Your veterinarian will best determine if your dog is responding as expected and if your dog should continue receiving Rimadyl. To report a suspected adverse reaction call Zoetis at 1-888-963-8471.

Issued October 2014

www.rimadyl.com © 2014 Zoetis Inc. 14029100
CAPSULES/CHEWABLE TABLETS

For oral use in dogs only

Do not use in cats.

Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans.

INFORMATION FOR THE OWNERS

Rimadyl is a non-steroidal anti-inflammatory drug (NSAID) that is rapidly and completely absorbed after oral dosing. It is marketed in a veterinary dosage form as a sterile injectable and a chewable tablet for dogs. The clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins and other related substances.

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REFERENCES


89. Deramax prescribing information, NADA 141-203, 2011.


