Unleashed

Canine osteoarthritis is a chronic, progressive, inflammatory disease. Left unchecked, the cycle of inflammation and pain can lead to chronic pain (wind-up) and ongoing joint damage, both of which become progressively more difficult to treat as they worsen. 

NSAIDs are a cornerstone of osteoarthritis management. For improved activity and quality of life, medical treatment of osteoarthritis should include the triad of weight control, exercise, and pharmacological management of inflammation and pain. NSAIDs break the progressive cycle of inflammation and pain by acting in both the joint and the dorsal horn. For most dogs, the benefits of using NSAIDs outweigh the risks.

RIMADYL offers pain relief dogs can feel, for improved activity you can see. RIMADYL reduces inflammation and pain in dogs with osteoarthritis so they can stay active. Administration is simple because dogs enjoy the palatability of RIMADYL chewable tablets and dosing is once daily. With more than 90 evidence-based articles, RIMADYL has established safety and efficacy and allows veterinarians to confidently prescribe the #1 NSAID.

Ongoing control of inflammation and pain for chronic osteoarthritis

Recent journal articles demonstrate that long-term use of NSAIDs (Innes et al), and specifically RIMADYL (Autefage et al), has clinical benefits, with a low risk of adverse events.

References

*Clinical studies conducted in companion animals.

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Osteoarthritis (OA) inflammation and pain: A progressive cycle of deterioration

- Involves the entire joint
- Ongoing inflammation
- Progressive degradation
- Chronic pain
- Decreased activity
- An overall negative impact on the patient

Osteoarthritis involves all components of the joint

Osteoarthritis affects as many as 20% of dogs in the US and is one of the most common sources of canine pain.1,2
Break the cycle of osteoarthritis with a comprehensive approach

Goals of osteoarthritis therapy are to decrease inflammation and pain, resulting in:

- Increased activity\(^3,4\)
- Preserved muscle mass and strength
- Regained function

Medical treatment of osteoarthritis should include the triad of weight control, exercise, and pharmacological management of inflammation and pain for an improved quality of life.\(^5\)

If properly treated, the progression of osteoarthritis can be slowed.\(^6\)

* Non-Steroidal Anti-Inflammatory Drug (NSAID).

Most veterinarians believe that osteoarthritis is under-diagnosed and under-treated.\(^7\)
Mechanism of disease

In osteoarthritis, the initial damage to the cartilage causes the release of cartilage degradation products, and injury to the chondrocytes result in release of matrix metalloproteinases (MMPs). MMPs are catabolic enzymes that cause additional damage to the cartilage.

MMPs and cartilage degradation products stimulate synoviocytes to release pro-inflammatory mediators, such as cytokines and prostaglandins.

In canine osteoarthritis, inflammation not only causes pain, but also contributes to irreversible joint damage.¹¹
Prostaglandins and other pro-inflammatory mediators initiate and maintain 2 cycles:

**Inflammatory cycle**\(^2,9,11-13\)
- Pro-inflammatory mediators cause further damage to the cartilage, resulting in the release of MMPs and cartilage degradation products
- The inflammatory cycle is perpetuated when MMPs and cartilage degradation products stimulate additional release of pro-inflammatory mediators
- If left untreated, inflammation eventually causes irreversible damage to cartilage, subchondral bone, synovium, and joint capsule

**Pain cycle**\(^14\)
- Inflammation causes the initial pain through stimulation of joint nociceptors
- As more overt biochemical changes occur in the joint, mechano-receptors are engaged and contribute to pain
- Pain can contribute to the disease process of osteoarthritis through neurogenic inflammation\(^15,16\)

**Persistent, uncontrolled pain leads to chronic peripheral and central hypersensitization, also known as wind-up pain**

<table>
<thead>
<tr>
<th>Components of wind-up pain</th>
<th>Consequences of wind-up pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amplification</td>
<td>• Difficult to treat</td>
</tr>
<tr>
<td>• Allodynia</td>
<td>• Often only managed, not eliminated</td>
</tr>
<tr>
<td>• Lower activation threshold</td>
<td>• Reoccurs without additional trauma</td>
</tr>
<tr>
<td>• Activation of wide dynamic range neurons (WDR)</td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology of OA
Diagnosis and treatment of chronic pain is challenging

Diagnosis

Although pain is the hallmark clinical sign of osteoarthritis, it can be subtle and often goes unnoticed. Some challenges of diagnosing chronic pain:

- Dog owners often do not mention it as a problem
  - Might not recognize subtle signs
  - Attribute subtle changes to “old age” or “slowing down”
- Because dogs mask pain, the degree of pain may not be appreciated during physical examination

Treatment

Since wind-up is more difficult to treat, one treatment modality may not control the multiple receptors that have been activated in chronic pain. This adds to the complexity of treating chronic osteoarthritis.

Optimal management of osteoarthritis should focus on early and continuous treatment.

**NSAIDs: A cornerstone of osteoarthritis management**

An important goal of osteoarthritis treatment is to break the progressive cycle of inflammation and pain. Prostaglandins contribute to inflammation, pain, and loss of function of the affected joint. By selectively blocking the release of prostaglandins, NSAIDs decrease inflammation and provide analgesia in the joint. NSAID activity also provides pain relief in the dorsal horn.
Assessing the benefits and risks of NSAID use\textsuperscript{18,19}

For the majority of patients, the benefits of using NSAIDs will outweigh the risks. However, the risk-benefit analysis of using NSAIDs should be determined on a patient-to-patient basis. There are 2 major categories of adverse events (AEs):

**Inducible**
- Reactions are dose related
- Reactions are attributable to the mechanism of action of the drug
- Predictable

**Idiosyncratic**
- Not dose related
- Not attributable to the mechanism of action of the drug
- Unpredictable and rare

The most common AEs seen with NSAIDs are inducible and include gastrointestinal irritation.\textsuperscript{20} Idiosyncratic reactions occur infrequently (≤1 in 10,000) and are more likely to appear in the first 5 to 90 days of treatment.\textsuperscript{18}

Though individual patient response may vary, the benefits of treating with an NSAID most often outweigh the risks for the majority of dogs.\textsuperscript{4,21}

**Clinical considerations when prescribing NSAIDs**
- Review history of previous medications and medical conditions
- Perform a thorough physical exam
- Screen the patient for any underlying conditions
- Inform the owner of potential risks and benefits
- Distribute client information sheets
- Use the lowest label dose that achieves an effective response
- Monitor individual response to determine appropriate duration of treatment
RIMADYL: Inflammation and pain relief unleashed

Effective treatment

- Indicated for the relief of inflammation and pain associated with osteoarthritis in dogs
- Reduces pain in dogs with osteoarthritis so they can stay active\(^{3,4}\)
- Also indicated for the control of postoperative pain associated with soft-tissue orthopedic surgeries in dogs

Effective dosing

- The FDA-approved safe and effective dose of RIMADYL is 2 mg/lb (4.4 mg/kg) once daily
- Once-daily dosing improves compliance among pet owners\(^{23}\)
- More dosing options than any other NSAID
- Dogs enjoy the palatability of RIMADYL chewable tablets\(^{22,24}\)

<table>
<thead>
<tr>
<th>Weight (lbs)</th>
<th>5-10</th>
<th>11-15</th>
<th>16-20</th>
<th>21-30</th>
<th>31-40</th>
<th>41-60</th>
<th>61-90</th>
<th>91-120</th>
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<tbody>
<tr>
<td>Once Daily Dosage</td>
<td>1/2 Tab</td>
<td>1 Tab</td>
<td>1/2 Tab</td>
<td>1 Tab</td>
<td>1/2 Tab</td>
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<td>1 Tab</td>
<td>1 1/2 Tabs</td>
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<tr>
<td></td>
<td>25 mg</td>
<td>25 mg</td>
<td>75 mg</td>
<td>100 mg</td>
<td>75 mg</td>
<td>100 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

In a study conducted by the American Animal Hospital Association (AAHA), dog owners reported that chewable tablets were the easiest formulation to administer.\(^{25}\)
An established efficacy and safety record

- RIMADYL has been used to safely treat more than 16 million dogs
- With more than 90 evidence-based articles published in peer-reviewed journals, RIMADYL has established safety and efficacy and allows veterinarians to confidently prescribe the #1 NSAID

*Clinical studies conducted in companion animals.

RIMADYL is the only NSAID FDA approved for use in dogs as young as 6 weeks old.

†Safe use of RIMADYL in animals less than 6 weeks of age, in pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established.

A trusted partner

- Zoetis, Inc. is fully committed to veterinarians and dedicated to continuing to build a diverse and innovative portfolio of first-in-class prescription medicines, such as RIMADYL
- RIMADYL was the first NSAID approved for canine use and has been a trusted NSAID to veterinarians since 1997

Important Safety Information

As with other NSAIDs, rare but serious side effects involving the digestive system, kidneys, or liver may occur. Regular monitoring is required for pets on medication. Pet owners should be advised to discontinue RIMADYL therapy if side effects occur and to contact their veterinarian. Refer to the full prescribing information for complete details.
“Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis”21

- Long-term was defined as 28 to 120 days of continuous treatment
- Published studies were evaluated based on the strength of scientific evidence
  - Only 15 peer-reviewed articles met the evaluation criteria
- Of these 15 articles, 10 included carprofen
- Safety, efficacy, progressive decrease in pain, progressive tolerance over time, altered disease progression, and an increase (or decrease) in adverse events were evaluated

<table>
<thead>
<tr>
<th>NSAID</th>
<th>FUNCTIONAL EFFICACY STUDIED</th>
<th>SAFETY STUDIED</th>
<th>TREATMENT PERIOD</th>
<th>NUMBER OF DOGS</th>
<th>NUMBER OF DOGS COMPLETING STUDY</th>
<th>REFERENCE</th>
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<tbody>
<tr>
<td>Carprofen</td>
<td>YES</td>
<td>YES</td>
<td>84 days</td>
<td>805</td>
<td>750</td>
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<tr>
<td>Firocoxib and carprofen</td>
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<td>YES</td>
<td>30 days</td>
<td>218</td>
<td>202</td>
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<td>YES</td>
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<td>YES</td>
<td>28 days</td>
<td>16</td>
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<td>Pelletier and others (2000)</td>
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<td>YES</td>
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<td>YES</td>
<td>YES</td>
<td>28 days</td>
<td>6</td>
<td>6</td>
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<td>YES</td>
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<td>Deracoxib and aspirin</td>
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<td>24</td>
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<tr>
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<td>YES</td>
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<tr>
<td>Licofelone</td>
<td>YES</td>
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<td>28 days</td>
<td>16</td>
<td>13</td>
<td>Mansa and others (2007)</td>
</tr>
</tbody>
</table>

* Not all products evaluated in these studies are approved by the FDA for use in companion animals. Zoetis, Inc. does not recommend use of any product in an extra label manner.

† RIMADYL is approved in the USA for use in dogs for the relief of pain and inflammation associated with osteoarthritis and control of postoperative pain associated with soft tissue and orthopedic surgeries at the dose of 4.4 mg/kg (2 mg/lb) body weight. In some of these studies, carprofen was used at the lower European dose of 4.0 mg/kg body weight.
Results

- Of the 15 articles reviewed, 7 compared efficacy over time
  - 6 showed progressive improvement
  - 1 showed no difference
- There was **no significant correlation** between study length and experimental (adverse) event rate

“...the current evidence suggests that there is a clinical benefit of longer-term NSAID use for dogs with chronic osteoarthritis and that this is associated with a low risk of serious adverse events.”


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“Efficacy and safety of long-term oral administration of carprofen in the treatment of osteoarthritis in dogs”

- 110 dogs with chronic signs of osteoarthritis were administered RIMADYL once daily for 120 days*

**Results**

**Veterinary investigators**

- The percentage of dogs showing a positive treatment effect increased from 12% on Day 5 to 74% on Day 120
- Mean Visual Analog Scale (VAS) scores for the 4 clinical parameters assessed by the veterinary investigators significantly decreased throughout the study ($P \leq 0.05$)

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Pet owners

- Owners also observed a continuous and steady improvement of the following 6 parameters
  - Going up and down stairs
  - Walking
  - Standing up or lying down
  - Playing or doing physical exercise
  - Running
  - Jumping

- The improvements observed by owners were comparable to what was observed by the veterinary investigators

Other clinical observations

- Gastrointestinal undesirable effects likely to be related to carprofen, but with no harmful consequences, were observed in 5% of the treated dogs

- No detrimental effects of the treatment of hematological, renal, and hepatic parameters were observed

“...the long-term administration of carprofen provides a steadily increasing improvement of clinical signs of osteoarthritis in dogs and does not result in an increase of the incidence of suspected adverse reactions.”


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References


7. Proprietary Market Research, Zoetis, Inc.


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Ongoing control of inflammation and pain for chronic osteoarthritis

Recent journal articles demonstrate that long-term use of NSAIDs (Innes et al), and specifically RIMADYL (Autefage et al), has clinical benefits, with a low risk of adverse events.3,21

RIMADYL®
(carprofen)

A daily dose of pain relief
RIMADYL® (carprofen)

Caplets/Cheewal Tablets
For oral use in dogs only
Sterile Injectable Solution 50 mg/mL
For subcutaneous use in dogs only
Non-steroidal, anti-inflammatory drug

CAUTION: Federal law restricts this drug to use in or on a licensed veterinarian.

DESCRIPTION: RIMADYLL carprofen is a non-steroidal, anti-inflammatory drug (NSAIID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the non-proprietary designation for a substituted carbonyls, 2-aryl-methyl-5-arylcarboxylic-3-oxo-acid. The empirical formula is C26H22Cl2N2O3 and the molecular weight is 434.3. The chemical structure of carprofen is as follows: Carprofen is a white, crystalline compound. It is freely soluble in ethanol, but practically insoluble in water.

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase. Two unique cyclooxygenase isozymes have been identified, COX-1 and COX-2. COX-1 is the predominantly expressed enzyme in normal gastrointestinal tissue whereas COX-2 is the isozyme that is inducible by pro-inflammatory cytokines and is involved in the inflammatory process. Inhibition of COX-2 is associated with anti-inflammatory activity while inhibition of COX-1 is associated with gastrointestinal toxicity. The selective inhibition of COX-2 by carprofen results in inhibition of the production of prostaglandins involved in inflammation. Inhibition of COX-1 is associated with increased risk of peptic ulceration.

Although some studies have demonstrated that carprofen has moderate inhibition of both COX-1 and COX-2 enzymes, there is no specific information on COX-1 and COX-2 inhibition in vivo. A number of studies have shown that carprofen inhibits the production of prostanoids elicited by a wide range of stimuli in vivo in normal and inflamed tissues and in isolated cells. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-2 is associated with anti-inflammatory activity while inhibition of COX-1 is associated with increased risk of gastrointestinal ulceration. Therefore, the anti-inflammatory activity of carprofen is associated with the selective inhibition of COX-2.

Gastrointestinal: carprofen is a non-steroidal, anti-inflammatory agent with characteristic analgesic and antiinflammatory activity, most frequently reported as nausea or vomiting, lethargy, incoordination, seizure, or behavioral changes. These effects were most common at higher doses of carprofen (5 mg/lb or higher), and in dogs with underlying gastrointestinal disease.

Facial swelling, hives, erythema.

Swelling 0 1.2
Dermatologic:

Erythema 0 0.7
Edema 0 1.3
Erythema multiforme 0 0.3
Facial swelling, hives, erythema.

The effects of prostaglandin synthesis inhibition on the immune response.

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