

Carprofen

**BRAND NAME: RIMADYL, NOVOX, VETPROFEN
(ZENECARP IN THE U.K.)**

AVAILABLE IN
25 mg, 50 mg & 100 mg
CAPLETS

BACKGROUND

Carprofen is a member of the class of drugs known as NSAIDs (non-steroidal anti-inflammatory drugs), the same class as such common over-the-counter remedies as Advil (Ibuprofen), Aleve (Naproxen), Orudis (ketoprofen), and Aspirin as well as more controversial prescription drug such as Celebrex (celecoxib) and Vioxx (rofecoxib) . This class of drug is used for pain relief successfully in humans but the development of safe NSAIDs for dogs has only been achieved relatively recently and continues to be problematic in the cat. With the possible exception of aspirin, none of the human drugs listed above can be safely used in pets.

The problem with this class of drugs has been unacceptable (even life-threatening) side effects. Problems have in the past been related to:

- Stomach ulceration - even perforation and rupture of the stomach can occur. This is not only painful but potentially lethal.
- Platelet deactivation - platelets are the cells controlling the ability to clot blood and, as a general rule, it is preferable not to promote bleeding.
- Decreased blood supply to the kidney - this could tip a borderline patient in to kidney failure.

The veterinary profession has been in need of an NSAID that could effectively relieve pain without the above risks. In 1997, Pfizer Animal Health released carprofen for dogs in the U.S. as the answer to this need. This medication had been available in the U.K. since 1994 and has earned a reputation for effectiveness and safety.

This new plane of safety is made possible by new scientific knowledge. Inflammatory biochemicals responsible for the pain and inflammation we want to alleviate are produced by an enzyme called "cyclo-oxygenase 2." The goal is to inhibit this enzyme without inhibiting its counterpart "cyclo-oxygenase 1." Cyclo-oxygenase 1, abbreviated COX-1, is what is called a "constitutive" enzyme. This means it is involved in producing regulatory biochemicals (called "prostaglandins") which are important in maintaining the normal health and function of our bodies. We want to leave this enzyme alone. Cyclo-oxygenase 2, abbreviated COX-2, produces inflammatory biochemicals but also is important in regulating kidney blood flow and in some reproductive and central nervous system function.

While the products of COX-2 are not only harmful ones, the chief effect of COX-2 seems to be facilitating pain, swelling, redness, etc. In the past, NSAIDs could not distinguish the COX enzymes; they inhibited them both. With the development of "COX preferential" and "COX selective" NSAIDs, we can inhibit COX-2 and leave COX-1 alone. The introduction of COX-2 preferential NSAIDs has reduced stomach and intestinal side effects by 50% in humans and has made FDA approval of certain NSAIDs possible for pets.

It is probably worth mentioning that the COX-1/COX-2 relationship is not as simple as considering COX-1 to be good and COX-2 to be bad. It turns out there is actually a COX-3 and that COX-2 has some constitutive effects that should be preserved. Still, the ability for a drug to effect COX-2 more than COX-1 has been extremely beneficial to humans as well as pets.

HOW THIS MEDICATION IS USED

Carprofen is used in the treatment of pain either for short term or long term use. As of December 2001, Carprofen has been licensed for once a day use (ie the dose for the entire day can be given all at once). It is just as effective to employ the products original directions and divide the daily dose into an AM and PM administration, breaking the full daily dose into two half doses.

A dog that is potentially a candidate for long term use of carprofen should have a complete examination by the veterinarian, a screening blood panel to establish baseline biochemical values, and ideally some kind of recheck testing two weeks after starting carprofen. This is because most adverse reactions, unusual as they may be, occur within this initial time frame and it is important that they be recognized before they get out of hand. After this initial period, complete blood panels should be screened every six months, an important step with any medication for long term use, not just the NSAIDs.

Carprofen is approved only for canine use officially and was designed for long term use in dogs. **Do not use this medication in a cat without specific veterinary guidance.** At this time use of NSAIDs for pain management in the cat is limited to meloxicam and is not approved by the FDA.

SIDE EFFECTS

The side effects of concern are the same with all NSAIDs: stomach ulceration, loss of kidney function, and inappropriate bleeding. These are dependent on the dose of medication used and on risk factors of the host (for example: an aged pet may not efficiently clear a dose of medication from its body leading to stronger and longer activity of the drug). There is also a particular idiosyncratic reaction for NSAIDs which has received a great deal of press. An idiosyncratic reaction is one that is not dose-dependent nor predictable by any apparent host factor; it simply happens out of the blue. This particular idiosyncratic reaction is a liver toxicity (see the Hepatopathy side effect below), which is rare enough so as not to show up in any of the initial 400 test subjects, nor in the U.K. and was not recognized until carprofen was used in over a million dogs. We will review this reaction and others below.

- There is an approximately one in 1000 chance of a dog on carprofen developing nausea, appetite loss, vomiting or diarrhea. If any of the above are noted, carprofen should be discontinued and the dog brought in for a liver enzyme blood test. In most cases, the reaction is minor and resolves with symptomatic relief, but it is important to rule out whether or not the patient has more than just a routine upset stomach.
- If a patient has borderline kidney function, NSAIDs should not be used as they reduce blood flow through the kidneys. It is also important that NSAIDs not be given to dehydrated patients because of this potential side effect.
- **The Hepatopathy Side Effect (usually occurs within the first 3 weeks of use)**
A carprofen reaction that has received special attention is hepatopathy, a type of liver disease. Symptoms include nausea, appetite loss, and/or diarrhea as well as marked elevations (3-4 times higher than the normal range) in liver enzymes measured in the blood.

Dogs with this syndrome show improvement with support 5 - 10 days after discontinuing carprofen. It is important that carprofen be discontinued and the patient evaluated in the event of upset stomach signs in case of this syndrome. Even though this is a rare syndrome (one in 5000), it can become life-threatening if ignored. Appetite loss or other intestinal signs do not necessarily indicate a hepatopathy but since they might, it is important not to ignore these signs should they occur. There is no way to predict which dogs will experience this side effect.

The hepatopathy reaction usually occurs in the first 3 weeks after starting carprofen but could theoretically occur later.

- All NSAIDs are removed from the body by the liver. If the patient's liver is not working normally due to another disease or if the patient is taking other drugs that are also removed by the liver, it is possible to "over work" the liver and exacerbate pre-existing liver disease. If there is any question about a patient's liver function, another class of pain reliever should be selected.

It is important to realize that COX-selectivity is not the sole factor in safety. In humans, the incidence of kidney function-related side effects was unchanged by the development of COX-2 preferential NSAIDs and we expect the same is true with dogs. Still, these drugs have an excellent track record for safety; the important issue is to recognize risk factors for adverse reactions and take preventive steps (see the Concerns and Cautions section below). Many exaggerated reports and rumors have surfaced on the internet and it is important to consider only confirmed and properly investigated information.

INTERACTIONS WITH OTHER DRUGS

Multiple drugs of the NSAID class should not be used concurrently as the potential for the aforementioned side effects increases. For similar reasons, NSAIDs should not be used in conjunction with corticosteroid hormones such as prednisone, dexamethasone etc. Pfizer recommends a 5-7 day rest period when changing over to carprofen or to another NSAID from carprofen. Aspirin poses an exception due to its strong platelet inactivating abilities so 10-14 days is recommended when switching to carprofen from aspirin. Allow at least one week between prednisone and carprofen.

If carprofen is used concurrently with phenobarbital, it is especially important that appropriate liver monitoring be performed. (Our hospital recommends bile acids testing every 6 months for dogs on phenobarbital.) These two drugs interact such that neither may work well if they are used together.

ACE inhibitors such as enalapril or benazepril may not be as effective in the presence of carprofen (ACE inhibitors are used in the treatment of hypertension or heart failure). This is because ACE inhibitors depend on the dilation of blood vessels in the kidneys and such dilation can be interfered with by NSAIDs).

In 9% of all adverse reactions reported regarding carprofen, concurrent use with corticosteroids was reported.

CONCERNS AND CAUTIONS

Carprofen is available as a chewable tablet which is highly palatable to animals. This increases the potential for accidental overdose should a pet gain access to a large amount of chewable tablets. Keep chewable carprofen out of the reach of children and pets.

Carprofen has not been tested in pregnant or nursing females and thus is not recommended for use in such individuals, particularly since COX-2 is important in reproductive function. This also means that pregnant women might do well not handling this medication.

Carprofen should not be used in dogs with pre-existing liver or kidney disease. In order to screen for pre-existing liver or kidney disease it is a good idea to run a blood chemistry panel prior to starting long term carprofen.

ANY DOG ON LONG TERM MEDICATION OF ANY KIND SHOULD PROBABLY HAVE BLOOD CHEMISTRY RECHECKS EVERY 6 MONTHS.

The blood pressure related side effects that have made COX-2 selective NSAIDs controversial in humans are not significant factors in canine use.

Carprofen should not be used in patients with pre-existing GI ulcerations.

Carprofen has been tested for safety in puppies as young as 6 weeks of age but not younger. It should not be used in puppies less than six weeks of age.



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Additional drug and general pet care information can be found on our world wide web site:
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