

Meloxicam

**BRAND NAME: MELONEX, METACAM, MOBIC,
MOBICOX, OROCAM**

AVAILABLE IN
7.5 & 15 mg TABLETS
(HUMAN FORMULATIONS)
TRANSMUCOSAL SPRAY
& TWO STRENGTHS
OF ORAL SUSPENSION
(VETERINARY FORMULATIONS)

BACKGROUND

Metacam 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), and aspirin. This class of drug is used for pain relief successfully in humans but the development of safe NSAIDs for pets has only been achieved relatively recently.

- Stomach ulceration - even perforation and rupture of the stomach can occur. This is not only painful but life-threatening.
- Platelet deactivation - platelets are the cells controlling the ability to clot blood and, as a general rule, it is preferable not to promote bleeding. We would prefer platelets to remain active and able to function should we need them.
- Decreased blood supply to the kidney - this could tip a borderline patient in to kidney failure.

The veterinary profession had been in need of an NSAID that could effectively relieve pain without the above risks. In 1997, Pfizer Animal Health released the first NSAID for dogs in the U.S. as the answer to this need. This product was carprofen which had been available in the U.K. since 1994 and has earned a reputation for effectiveness and safety. Meloxicam has only been approved in the U.S. for canine use since 2003 but has been available in Canada and Europe for years before. (Meloxicam has been available in the U.S. for human use for many years but not in a format that lends itself to safe pet use -see the Concerns and Cautions section below regarding pet use of the human formula.)

This new plane of safety for pets was made possible by new biochemical knowledge. Inflammatory biochemicals responsible for the pain and inflammation we want to alleviate are produced by an enzyme called "cyclo-oxygenase 2" or simply "COX-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 inflammation but also is important in regulating kidney blood flow and in some reproductive and central nervous system function. We want to inhibit COX-2 in such a way that we do not disrupt its healthful functions.

In the past, NSAIDs could not distinguish the COX enzymes and 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.

HOW THIS MEDICATION IS USED

Meloxicam is generally given to control arthritis pain in dogs though can be given for many other painful conditions such as injuries, cancer, surgery, dental infections, and more. In dogs, it is typically given as a once a day as a pleasantly flavored liquid. The veterinary approved product comes with a special dosing syringe marked to show how much to give for the pet's weight (rather than in milliliters as most syringes are marked).

Feline use of meloxicam is of some controversy. In Europe, Canada, Australia and New Zealand, long term use of the 0.5 mg/ml meloxicam formula in cats is registered, approved, and heavily marketed; however, this formula is not legally approved for cats in the United States. Further, the manufacturer has specifically discouraged feline use of meloxicam beyond its approved use in the U.S. (one dose for post surgical pain relief). This paradox of marketing the product one way for most of the world and another way in the U.S. has been frustrating as there are substantially fewer oral pain relief options for cats available compared to what is available for dogs. Meloxicam is still used by many veterinarians for cats but the advent of robenacoxib for cats has provided a less controversial feline NSAID.

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 that has received a great deal of press. An idiosyncratic reaction is one that is neither dose-dependent nor predictable by any apparent host factor; it simply happens out of the blue. This particular idiosyncratic reaction is a liver toxicity that is rare enough that it did not show up in any of the initial 400 carprofen test subjects, nor in the U.K., and was not recognized until carprofen was used in over a million dogs in the U.S. after its release as the first NSAID. We will review this reaction below. While originally it was carprofen use that led to the recognition of this reaction, it is now felt that all veterinary NSAIDs have potential to cause this reaction.

- The most common side effects of meloxicam are nausea, appetite loss, vomiting or diarrhea. If any of the above are noted, meloxicam should be discontinued and the pet brought in for a liver enzyme and renal parameter 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. This is particularly true in the cat.
- The Hepatopathy Side Effect (usually occurs within the first 3 weeks of use)
An NSAID 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. The question of whether other veterinary NSAIDs share this reaction has arisen. At this time, it is generally felt that the hepatopathy idiosyncratic reaction is not unique to carprofen and should be of concern with any veterinary NSAID and this includes meloxicam. This reaction seems to be a canine issue only.

Dogs with hepatopathy show improvement with support 5 to 10 days after discontinuing medication. It is important that the NSAID 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, such as meloxicam, 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).

One might wonder how this is possible given the COX-2 selectivity and the answer is complex. While it is easy to think of COX-2 as the "bad" enzyme, COX-1 as the "good" enzyme, and COX selectivity as seeing that only the "bad" enzyme is suppressed, this kind of thinking would be a drastic over-simplification. In fact, COX-2 is important in activities involving the healing of stomach ulcers and other important processes. There is also a COX-3, of which very little is known, and studies show there may very well be a COX-4. Further, at higher doses, meloxicam and other COX-2 selective NSAIDs will lose their COX-2 selectivity and significantly inhibit COX-1 as well.

INTERACTIONS WITH OTHER DRUGS

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. Poets (formerly Pfizer Animal Health) recommends a 5 to 7 day rest period when changing from one NSAID to another. Aspirin poses an exception due to its strong platelet inactivating abilities so 10 to 14 days is recommended when switching to another veterinary NSAID from aspirin. Allow at least one week between prednisone and meloxicam.

If meloxicam is used concurrently with phenobarbital, it is especially important that appropriate liver monitoring be performed. 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 meloxicam. (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).

Concurrent use of diuretics may increase the potentially for kidney toxicity.

CONCERNS AND CAUTIONS

Meloxicam works as well when given on an empty stomach as when given on a full stomach. If a patient has had some upset stomach issues with meloxicam these can often be minimized by administering the drug on a full stomach.

Maximum effect is seen approximately 8 hours after administration. When beginning a trial course of meloxicam, a response may take 3 or 4 days to show. If no response has been seen in 10 days, meloxicam has failed and a different pain medication should be tried. If one NSAID fails, another may well work.

The veterinary formulations of meloxicam are oral liquids (either 1.5mg/ml or 0.5 mg/ml). The liquid formulation allows for accuracy in dosing. The human tablets are available in much higher strengths and will be inappropriate except possibly for very large dogs. It is important not to use human medications on pets unless your veterinarian has provided detailed dosing instructions.

Meloxicam should not be used in pregnancy or in lactation.

Meloxicam can be used in cats but with caution (see above regarding use in countries outside the U.S.). The original oral solution of meloxicam was commonly dosed in drops from the bottle. Since the wrong dose of meloxicam can be very dangerous for cats, it is important not to drop the drops directly into the cat's mouth from the bottle as squeezing too strongly could easily deliver an overdose. The low dose (0.5 mg/ml) formula can be dosed with the provided syringe. In the cat this product is given either as a single one time injection in association with surgery (its FDA approved use) or long term 2-3 times per week (its non-U.S. dose). Long term use of this product in cats is "off label" in the U.S.

As with all veterinary NSAIDs periodic monitoring tests are important to check liver enzymes and kidney function, and to generally screen the patient's health. Typically an every 6 months schedule is recommended for dogs. There is no general consensus on what is appropriate for cats but because of feline sensitivity towards NSAIDs, feline monitoring is especially important. If you are using this product in the cat, be sure you understand what monitoring schedule your veterinarian is recommending for your specific pet.

Patients being considered for long term meloxicam use should be evaluated with a complete physical examination and initial screening blood test to identify any factors, such as liver or kidney disease, that might preclude the use of this or any other NSAID.

Meloxicam should not be used in puppies under 6 months of age or kittens under 4 months of age (safety has not been proven).

Meloxicam should be avoided, if possible, in patients with impaired function of the liver, kidney or heart. It should also be avoided in dehydrated patients and patients with known GI ulcers.

ALWAYS SHAKE THE BOTTLE OF MELOXICAM BEFORE DRAWING UP THE DOSE

FOR MORE INFORMATION

The manufacturer of veterinary meloxicam (Boehringer Ingelheim) has launched a web site for more information at:

www.metacam.com

The Food and Drug Administration's page on veterinary non-steroidal anti-inflammatory drugs may be viewed at:

www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055434.htm

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

<http://www.marvistavet.com>