

Boehringer Ingelheim Vetmedica, Inc.



Technical Bulletin

Judicious use of NSAIDs: Titrating to the lowest effective dose

Introduction

Veterinary practitioners have long known the benefits of using non-steroidal anti-inflammatory drugs (NSAIDs) in their osteoarthritic patients. The relief of pain and inflammation provided by NSAIDs can significantly improve mobility and quality of life for patients.

Practitioners are also well aware of the potential risks associated with NSAID use, including gastrointestinal ulcers, liver disease, and kidney failure. Veterinarians have therefore learned to be judicious, balancing the need to relieve pain with the responsibility of doing so in a manner that poses the least amount of risk to patients.

While drug risk information is communicated to practitioners and the public through product labeling, clients whose pets experience adverse drug events often report having never received a client information sheet.¹ The FDA, in an effort to improve risk communication and consistency in labeling across the NSAID class, recently required drug manufacturers to include a statement in their product labeling about using the lowest effective dose of an NSAID for the shortest duration consistent with individual

response. Thus by titrating NSAIDs until the desired effect is seen, practitioners can achieve treatment goals while minimizing risk.

In addition to the FDA, veterinary professional groups like the American Animal Hospital Association and other leading experts equally support the practice of lowest effective dosing.² This dosing standard makes sense from a number of perspectives:

- It is simply good medicine to find the lowest dosage of many pharmaceutical drugs to achieve a desired clinical effect.
- Allowing clients to monitor their dog's progress and gradually administer a lower dosage of their pet's NSAID according to their veterinarian's instructions lets them take an active role in the health management program of their pet. It may also lead to significantly greater client satisfaction and compliance.
- Following the lowest effective dose principle can lead to greater cost efficiencies for clients long-term. Treating a chronic condition like arthritis can become expensive, so keeping medication costs down is another way to encourage client compliance.



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Use of Liquid NSAIDs to Achieve the Lowest Effective Dose

The principle of lowest effective dosing can be broken down into two primary components, both aimed at enhancing patient safety:

- Administer the label dose initially.
- Titrate to the lowest effective dose over time.

A liquid NSAID such as Metacam® (meloxicam) Oral Suspension can make it easier for practitioners and pet owners to do both. The liquid formulation with calibrated dosing syringe permits individualized dosing based on patient weight. The dose can be adjusted in very small, precise weight increments, which can be gradually decreased over time until the most appropriate maintenance dose has been reached. METACAM is also available in a special concentration for small dogs, making it even easier to titrate the dosage in dogs weighing less than 10 pounds.

Because METACAM allows practitioners to individualize the dosage for each patient, they offer a significant benefit over tablets. NSAIDs delivered in a rigid tablet form must be split to approximate weight levels in order to compensate for changes in a patient's body weight.

When tablets are split, the incremental changes can be significant, making precise weight-to-medication ratios difficult to achieve.



A Dosing Protocol for METACAM³

Just as using METACAM makes lowest effective dosing easier, so does following a standard dosing protocol. An example of an effective recommended protocol is provided below:

- Initiate therapy using labeled dose.
- Follow up with owner in 7 to 14 days to assess medication effectiveness.
- Maintain labeled dose for 2 to 3 weeks. How well the patient responds to therapy will determine the exact time until titration.
- Initiate titration based on the protocol in the table below.

| Dog weight | Titration | Maintenance schedule |
|---------------------|---|--|
| Under 10 lbs | Using the 0.5 mg/mL concentration of METACAM, decrease the amount in the dosing syringe by 1 lb per week until clinical signs start to reappear. | Monitor clinical signs. At the reappearance of any symptoms, maintain the patient long term at the dose just previous to when clinical signs reappeared. |
| Over 10 lbs | Using the 1.5 mg/mL concentration of METACAM, decrease the amount in the dosing syringe by 5 lbs per week until clinical signs start to reappear. | |

Owners of both small and large dogs need to be educated about an important fact: in times of a flare up of clinical signs, their pet can be moved back to the normal daily dose (though this dose should never be exceeded) for 2 to 3 days. After 2 to 3 days at the normal daily dose, with amelioration of clinical signs, the previously determined lowest effective dose can be re-instituted long term.

Confidence in METACAM Safety*



METACAM has the longest history of use worldwide—over 15 years in over 30 countries.³ During that time, millions of doses of METACAM have been delivered safely to control pain.³ In addition to this proven record of safe clinical use, data from a 6-month target animal safety trial demonstrated that no dogs developed acute renal failure, liver disease, or GI ulcers/perforations, even when administered up to 5 times the label dose.⁴ With its solid track record of safe use and its ability to be titrated easily to the lowest effective dose, METACAM is an NSAID that can be used with confidence.

References:

1. American Veterinary Medical Association website. Minimizing the risk factors associated with veterinary NSAIDs. Available at: <http://www.avma.org/onInews/javma/apr04/040415g.asp>. Accessed November 1, 2007.
2. Hellyer P, Rodan I, Brunt J, et al. AAHA/AAFP pain management guidelines for dogs and cats. *J Am Anim Hosp Assoc.* 2007;43:235-248.
3. Data on file, Boehringer Ingelheim Vetmedica, Inc.
4. METACAM Freedom of Information Summary, NADA 141-213.

*See Important Safety Information in this piece and accompanying Full Prescribing Information.

Achieving the Lowest Effective Dose with METACAM Oral Suspension: Two Case Studies

Grizzly

70-lb, male neutered Collie cross
10½ years old

The owners complained of general slowness, with difficulty rising and less of a willingness to go for walks. He is not displaying any other symptoms.

Physical examination: Normal except for moderate muscle atrophy in both hind limbs and a painful response to extension of the right hip.

Adjunct testing: Radiographs revealed degenerative joint disease in both hips (moderate in right, mild in left). Complete blood count, serum biochemical panel, and urinalysis were within normal limits.

Diagnosis: Pain due to coxofemoral osteoarthritis.

Treatment: Grizzly was started on METACAM Solution for Injection in the clinic at a dose of 0.09 mg/lb. He was prescribed METACAM Oral Suspension 1.5 mg/mL, and the owner was instructed to give the 70-lb dose via the calibrated dosing syringe once daily.

Phone conversation 6 days later: "Grizzly is greatly improved."

The following "titration schedule" was followed:

| Week | Dosage of METACAM given once daily using dosing syringe |
|------|---|
| 1-3 | 70 lb |
| 4 | 65 lb |
| 5 | 60 lb |
| 6 | 55 lb |
| 7 | 50 lb |
| 8 | 45 lb |
| 9 | 40 lb |
| 10 | 35 lb |
| 11 | 30 lb |

At the 30-lb dose, subtle signs of discomfort reappeared. Grizzly was slower to rise and seemed slightly less active. Thus, he was moved up to the previous dose (35 lbs), where he was maintained long term for 2 years. Approximately once a month, especially after an extra long walk, the owner has given the 70-lb dose for 2 to 3 days to relieve the flare-up of pain symptoms.

Misty

7-lb, female spayed Yorkshire Terrier
12½ years old

The owners' primary complaint was that Misty seemed to be "getting old." She is reluctant to go for walks and does not jump onto the bed like she used to. The owners noted no other problems.

Physical examination: All normal except for thickened stifles bilaterally (with no palpable laxity) and a decrease in hind limb musculature.

Adjunct testing: Radiographs revealed moderate degenerative joint disease in both stifle joints. Complete blood count, serum biochemical panel, and urinalysis were all within normal limits.

Diagnosis: Pain due to bilateral stifle osteoarthritis.

Treatment: Misty was started on METACAM Solution for Injection in the clinic at a dose of 0.09 mg/lb. She was prescribed the 0.5 mg/mL METACAM Oral Suspension, and the owner was instructed to give the 7-lb dose via the dosing syringe once daily.

Phone conversation 1 week later: "She is like a puppy again."

The following "titration schedule" was followed:

| Week | Dosage of METACAM given once daily using dosing syringe |
|------|---|
| 1-3 | 7 lb |
| 4 | 6 lb |
| 5 | 5 lb |
| 6 | 4 lb |
| 7 | 3 lb |

During week 7, signs of discomfort (reluctance to jump) reappeared. The owners were instructed to maintain Misty on the 4-lb dose of meloxicam once daily. She has done well for 18 months, though the owners have occasionally given Misty the 7-lb dose daily when she's shown increased signs of discomfort (about once every 2 months).

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Important Safety Information

As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, kidney, or liver side effects. The most common side effects reported in field studies were vomiting and soft stool/diarrhea. These are usually mild, but may be serious. If side effects occur, pet owners should halt therapy and contact their veterinarian. Pets should be evaluated for pre-existing conditions and currently prescribed medications prior to treatment with METACAM, then monitored regularly while on therapy. Concurrent use with another NSAID, corticosteroid, or nephrotoxic medication should be avoided or monitored closely. Please refer to the package insert for complete product information or visit www.thinkmetacam.com.

NADA 141-213, Approved by FDA

Metacam®

(meloxicam)

1.5 mg/mL Oral Suspension (equivalent to 0.05 mg per drop)
0.5 mg/mL Oral Suspension (equivalent to 0.02 mg per drop)

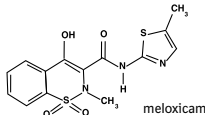
Non-steroidal anti-inflammatory drug for oral use in dogs only

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



Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxamic class. Each milliliter of Metacam Oral Suspension contains meloxicam equivalent to 0.5 or 1.5 milligrams and sodium benzoate (1.5 milligrams) as a preservative. The chemical name for Meloxicam is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The formulation is a yellowish viscous suspension with the odor of honey.



Indications: Metacam Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Dosage and Administration: Always provide client information sheet with prescription. Carefully consider the potential benefits and risk of Metacam and other treatment options before deciding to use Metacam. Use the lowest effective dose for the shortest duration consistent with individual response. Metacam Oral Suspension should be administered initially at 0.09 mg/lb (0.2 mg/kg) body weight only on the first day of treatment. For all treatments after day 1, Metacam Oral Suspension should be administered once daily at a dose of 0.045 mg/lb (0.1 mg/kg). The syringe is calibrated to deliver the daily maintenance dose in pounds.

Directions for Administration (1.5 mg/mL strength):

Dogs under 10 pounds (4.5 kg)

Shake well before use, then remove cap. Particular care should be given with regard to the accuracy of dosing. To prevent accidental overdosing of small dogs, administer drops on food only, never directly into the mouth. Carefully measure suspension onto food to assure that the correct dose is given before presentation of the food to the dog. The syringe provided with the meloxicam concentration of 1.5 mg/mL cannot be used to measure doses for dogs weighing less than 5 lbs (2.3 kg).

For dogs less than 5 lbs (2.3 kg), Metacam Oral Suspension can be given using the dropper bottle: one drop for each pound of body weight for the 1.5 mg/mL concentration (two drops for each kilogram of body weight), dropped directly onto the food.

For dogs between 5 - 10 pounds, Metacam Oral Suspension can be given by drops or by using the measuring syringe provided in the package (see dosing procedure below). The syringe fits on to the bottle and has a scale beginning at 5 lbs, designed to deliver the daily maintenance dose (0.05 mg/lb or 0.1 mg/kg). When using the syringe, the dog's weight should be rounded down to the nearest 5 pound increment. Replace and tighten cap after use.

Dogs over 10 pounds (4.5 kg)

Shake well before use then remove cap. Metacam Oral Suspension may be either mixed with food or placed directly into the mouth. Particular care should be given with regard to the accuracy of dosing. Metacam Oral Suspension can be given using the measuring syringe provided in the package (see dosing procedure below). The syringe fits on to the bottle and has a scale in pounds designed to deliver the daily maintenance dose (0.05 mg/lb or 0.1 mg/kg). When using the syringe, the dog's weight should be rounded down to the nearest 5 pound increment. Alternatively, Metacam Oral Suspension can be given using the dropper bottle: one drop for each pound of body weight for the 1.5 mg/mL concentration (two drops for each kilogram of body weight). Replace and tighten cap after use.

Directions for Administration (0.5 mg/mL strength):

Dogs under 10 pounds (4.5 kg)

Shake well before use, then remove cap. Particular care should be given with regard to the accuracy of dosing. To prevent accidental overdosing of small dogs, administer drops on food only, never directly into the mouth. Carefully measure suspension onto food to assure that the correct dose is given before presentation of the food to the dog. The syringe provided with the meloxicam concentration of 0.5 mg/mL cannot be used to measure doses for dogs weighing less than 1 lb (0.45 kg).

For dogs less than 1 lb (0.45 kg), Metacam Oral Suspension can be given using the dropper bottle: two drops for each pound of body weight for the 0.5 mg/mL concentration (five drops for each kilogram of body weight), dropped directly onto the food.

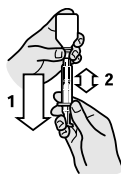
For dogs between 1-10 pounds, Metacam Oral Suspension can be given by drops or by using the measuring syringe provided in the package (see dosing procedure below). The syringe fits on to the bottle and has a scale beginning at 1 lb, designed to deliver the daily maintenance dose (0.05 mg/lb or 0.1 mg/kg). When using the syringe, the dog's weight should be rounded down to the nearest 1 pound increment. Replace and tighten cap after use.

Dogs over 10 pounds (4.5 kg)

Shake well before use then remove cap. Metacam Oral Suspension may be either mixed with food or placed directly into the mouth. Particular care should be given with regard to the accuracy of dosing. Metacam Oral Suspension can be given using the measuring syringe provided in the package (see dosing procedure below). The syringe fits on to the bottle and has a scale in pounds designed to deliver the daily maintenance dose (0.05 mg/lb or 0.1 mg/kg). When using the syringe, the dog's weight should be rounded down to the nearest 1 pound increment. Alternatively, Metacam Oral Suspension can be given using the dropper bottle: two drops for each pound of body weight for the 0.5 mg/mL concentration (five drops for each kilogram of body weight). Replace and tighten cap after use.



Shake bottle well. Push down and unscrew bottle top. Attach the dosing syringe to the bottle by gently pushing the end on to the top of the bottle.



Turn the bottle/syringe upside down. Pull the plunger out until the black line on the plunger corresponds to the dog's body weight in pounds.



Turn the bottle right way up and with a twisting movement separate the dosing syringe from the bottle.



Push the plunger to empty the contents of the syringe.

Contraindications: Dogs with known hypersensitivity to meloxicam should not receive Metacam Oral Suspension. Do not use Metacam Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.

Warnings: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. For oral use in dogs only. As with any NSAID all dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to and periodically during administration. Owner should be advised to observe their dog for signs of potential drug toxicity and be given a client information sheet about Metacam.

Precautions: The safe use of Metacam Oral Suspension in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concomitant administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after administration of the total daily dose of Metacam Oral Suspension, a non-NSAID or non-corticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of

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

Adverse Reactions: Field safety was evaluated in 306 dogs. Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetence) were the most common adverse reactions associated with the administration of meloxicam. The following table lists adverse reactions and the numbers of dogs that experienced them during the studies. Dogs may have experienced more than one episode of the adverse reaction during the study.

| Adverse Reactions Observed During Two Field Studies | | |
|---|-------------------|-----------------|
| Clinical Observation | Meloxicam (n=157) | Placebo (n=149) |
| Vomiting | 40 | 23 |
| Diarrhea/Soft Stool | 19 | 11 |
| Bloody Stool | 1 | 0 |
| Inappetence | 5 | 1 |
| Bleeding gums after dental procedure | 1 | 0 |
| Lethargy/Swollen Carpus | 1 | 0 |
| Epiphora | 1 | 0 |

In foreign suspected adverse drug reaction (SADR) reporting over a 9 year period, incidences of adverse reactions related to meloxicam administration included: auto-immune hemolytic anemia (1 dog), thrombocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

Post-Approval Experience (Rev. 2010): The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal ulceration

Urinary: azotemia, elevated creatinine, renal failure

Neurological/Behavioral: lethargy, depression

Hepatic: elevated liver enzymes

Dermatologic: pruritus

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with use of meloxicam in cats.**

To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for technical assistance, call 1-866-METACAM (1-866-638-2226). For a complete listing of adverse reactions for meloxicam reported to the CVM see: <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055394.htm>

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

Clinical Pharmacology: Meloxicam has nearly 100% bioavailability when administered orally with food. The terminal elimination half life after a single dose is estimated to be approximately 24 hrs (+/-30%) regardless of route of administration. There is no evidence of statistically significant gender differences in drug pharmacokinetics. Drug bioavailability, volume of distribution, and total systemic clearance remain constant up to 5 times the recommended dose for use in dogs. However, there is some evidence of enhanced drug accumulation and terminal elimination half-life prolongation when dogs are dosed for 45 days or longer.

Peak drug concentrations can be expected to occur within about 7.5 hrs after oral administration. Corresponding peak concentration is approximately 0.464 mcg/mL following a 0.2 mg/kg oral dose. The drug is 97% bound to canine plasma proteins.

Effectiveness: The effectiveness of meloxicam was demonstrated in two field studies involving a total of 277 dogs representing various breeds, between six months and sixteen years of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked studies were conducted for 14 days. All dogs received 0.2 mg/kg meloxicam on day 1. All dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study (n=109), dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all parameters. In the second field study (n=48), dogs receiving meloxicam showed a clinical improvement after 14 days of therapy for all parameters; however, statistical significance was demonstrated only for the overall investigator evaluation on day 7, and for the owner evaluation on day 14.

Palatability: Metacam Oral Suspension was accepted by 100% of the dogs when veterinarians administered the initial dose into the mouth. Metacam Oral Suspension was accepted by 90% of the dogs (123/136) when administered by owners. Problems associated with administration included refusal of food, resistance to swallowing and salivation.

Safety:

Six Week Study

In a six week target animal safety study, meloxicam was administered orally at 1, 3, and 5X the recommended dose with no significant clinical adverse reactions. Animals in all dose groups (control, 1, 3 and 5X the recommended dose) exhibited some gastrointestinal distress (diarrhea and vomiting). No treatment-related changes were observed in hematological, blood chemistry, urinalysis, clotting time, or buccal mucosal bleeding times. Necropsy results included stomach mucosal petechiae in one control dog, two dogs at the 3X and one dog at the 5X dose. Other macroscopic changes included areas of congestion or depression of the mucosa of the jejunum or ileum in three dogs at the 1X dose and in two dogs at the 5X dose. Similar changes were also seen in two dogs in the control group. There were no macroscopic small intestinal lesions observed in dogs receiving the 3X dose. Renal enlargement was reported during the necropsy of two dogs receiving the 3X dose and two receiving the 5X dose. Microscopic examination of the kidneys revealed minimal degeneration or slight necrosis at the tip of the papilla in three dogs at the 5X dose. Microscopic examination of the stomach showed inflammatory mucosal lesions, epithelial regenerative hyperplasia or atrophy, and submucosal gland inflammation in two dogs at the recommended dose, three dogs at the 3X and four dogs at the 5X dose. Small intestinal microscopic changes included minimal focal mucosal erosion affecting the villi, and were sometimes associated with mucosal congestion. These lesions were observed in the ileum of one control dog and in the jejunum of one dog at the recommended dose and two dogs at the 5X dose.

Six Month Study

In a six month target animal safety study, meloxicam was administered orally at 1, 3, and 5X the recommended dose with no significant clinical adverse reactions. All animals in all dose groups (controls, 1, 3, and 5X the recommended dose) exhibited some gastrointestinal distress (diarrhea and vomiting). Treatment related changes seen in hematology and chemistry included decreased red blood cell counts in seven of 24 dogs (four 3X and three 5X dogs), decreased hematocrit in 18 of 24 dogs (including three control dogs), dose-related neutrophilia in one 1X, two 3X and three 5X dogs, evidence of regenerative anemia in two 3X and one 5X dog. Also noted were increased BUN in two 5X dogs and decreased albumin in one 5X dog.

Endoscopic changes consisted of reddening of the gastric mucosal surface covering less than 25% of the surface area. This was seen in three dogs at the recommended dose, three dogs at the 3X dose and two dogs at the 5X dose. Two control dogs exhibited reddening in conjunction with ulceration of the mucosa covering less than 25% of the surface area.

Gross gastrointestinal necropsy results observed included mild discoloration of the stomach or duodenum in one dog at the 3X and in one dog at the 5X dose. Multifocal pinpoint red foci were observed in the gastric fundic mucosa in one dog at the recommended dose, and in one dog at the 5X dose.

No macroscopic or microscopic renal changes were observed in any dogs receiving meloxicam in this six month study. Microscopic gastrointestinal findings were limited to one dog at the recommended dose, and two dogs at the 3X dose. Mild inflammatory mucosal infiltrate was observed in the duodenum of one dog at the recommended dose. Mild congestion of the fundic mucosa and mild myositis of the outer mural musculature of the stomach were observed in two dogs receiving the 3X dose.

How Supplied:

Metacam Oral Suspension 1.5 mg/mL: 10, 32, 100 and 180 mL dropper bottles with measuring syringe.

Metacam Oral Suspension 0.5 mg/mL: 15 mL dropper bottles with measuring syringe.

Storage: Store at controlled room temperature 59-86°F (15 - 30°C).

Manufactured for:

Boehringer Ingelheim Vetmedica, Inc.

St. Joseph, MO 64506 U.S.A.

St. Patent 6,184,220

Metacam is a registered trademark of Boehringer Ingelheim Vetmedica GmbH, licensed to Boehringer Ingelheim Vetmedica, Inc.

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Code 601511, 601521, 601531, 601571/601411

Revised 07/2010

601501-00

10/2010

601307L-05-1006

Package Insert for Dogs

NADA 141-219, Approved by FDA

Metacam®

(meloxicam)

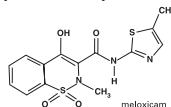
5 mg/mL Solution for Injection

Non-steroidal anti-inflammatory drug for use in dogs and cats only

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

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxamic class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, alcohol 15%, glycolufol 10%, poloxamer 188 5%, sodium chloride 0.6%, glycine 0.5% and meglumine 0.3%, in water for injection, pH adjusted with sodium hydroxide and hydrochloric acid.

**Indications:**

Dogs: Metacam (meloxicam) 5 mg/mL Solution for Injection is indicated in dogs for the control of pain and inflammation associated with osteoarthritis.

Dosage and Administration:

Carefully consider the potential benefits and risk of Metacam and other treatment options before deciding to use Metacam. Use the lowest effective dose for the shortest duration consistent with individual response.

Dogs: Metacam 5 mg/mL Solution for Injection should be administered initially as a single dose at 0.09 mg/lb (0.2 mg/kg) body weight intravenously (IV) or subcutaneously (SQ), followed, after 24 hours, by Metacam Oral Suspension at the daily dose of 0.045 mg/lb (0.1 mg/kg) body weight, either mixed with food or placed directly in the mouth.

Contraindications: Dogs with known hypersensitivity to meloxicam should not receive Metacam 5 mg/mL Solution for Injection.

Warnings: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. For IV or SQ injectable use in dogs. All dogs should undergo a thorough history and physical examination before administering any NSAID. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to, and periodically during use of any NSAID in dogs.

Owner should be advised to observe their dogs for signs of potential drug toxicity.

Precautions:

The safe use of Metacam 5 mg/mL Solution for Injection in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating bitches has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. Safety has not been established for intramuscular (IM) administration in dogs. When administering Metacam 5 mg/mL Solution for Injection, use a syringe of appropriate size to ensure precise dosing. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or preexisting disease that has not been previously diagnosed.

Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after the administration of the total daily dose of Metacam Oral Suspension, a non-NSAID or noncorticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with Metacam 5 mg/mL Solution for Injection has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Metacam 5 mg/mL Solution for Injection has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. The effect of cyclo-oxygenase inhibition and the potential for thromboembolic occurrence or a hypercoagulable state has not been studied.

Adverse Reactions:

Dogs: A field study involving 224 dogs was conducted. Based on the results of this study, GI abnormalities (vomiting, soft stools, diarrhea, and inappetence) were the most common adverse reactions associated with the administration of meloxicam. The following table lists adverse reactions and the numbers of dogs that experienced them during the study. Dogs may have experienced more than one episode of the adverse reaction during the study.

| Adverse Reactions Observed During Field Study | | |
|---|--------------------|-------------------|
| Clinical Observation | Meloxicam (n =109) | Placebo (n = 115) |
| Vomiting | 31 | 15 |
| Diarrhea/Soft Stool | 15 | 11 |
| Inappetence | 3 | 0 |
| Bloody Stool | 1 | 0 |

In foreign suspected adverse drug reaction (SADR) reporting, adverse reactions related to meloxicam administration included: auto-immune hemolytic anemia (1 dog), thrombocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

Post-Approval Experience (Rev. 2009):

The following adverse reactions are based on post-approval adverse drug event reporting. The categories are listed in decreasing order of frequency by body system:

Gastrointestinal: *vomiting, diarrhea, melena, gastrointestinal ulceration*

Urinary: *azotemia, elevated creatinine, renal failure*

Neurological/Behavioral: *lethargy, depression*

Hepatic: *elevated liver enzymes*

Dermatologic: *pruritus*

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with the use of meloxicam in cats.**

To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for technical assistance, call 1-866-METACAM (1-866-638-2226).

For a complete listing of adverse reactions for meloxicam reported to the CVM see:

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055394.htm>

Information For Dog Owners: Meloxicam, like other NSAIDs, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with NSAID intolerance. Adverse reactions may include vomiting, diarrhea, lethargy, decreased appetite and behavioral changes. Dog owners should be advised when their pet has received a meloxicam injection. Dog owners should contact their veterinarian immediately if possible adverse reactions are observed, and dog owners should be advised to discontinue Metacam therapy.

Clinical Pharmacology: Meloxicam has nearly 100% bioavailability when administered orally or after subcutaneous injection in dogs. The terminal elimination half life after a single dose is estimated to be approximately 24 hrs (+/-30%) in dogs regardless of route of administration. Drug bioavailability, volume of distribution, and total systemic clearance remain constant up to 5 times the recommended dose for use in dogs. However, there is some evidence of enhanced drug accumulation and terminal elimination half-life prolongation when dogs are dosed for 45 days or longer.

Peak drug concentrations of 0.734 mcg/mL can be expected to occur within 2.5 hours following a 0.2 mg/kg subcutaneous injection in dogs. Based upon intravenous administration in Beagle dogs, the meloxicam volume of distribution in dogs (Vd_l) is approximately 0.32 L/kg and the total systemic clearance is 0.01 L/hr/kg. The drug is 97% bound to canine plasma proteins.

Effectiveness:

Dogs: The effectiveness of Metacam 5 mg/mL Solution for Injection was demonstrated in a field study involving a total of 224 dogs representing various breeds, all diagnosed with osteoarthritis. This placebo-controlled, masked study was conducted for 14 days. Dogs received a subcutaneous injection of 0.2 mg/kg Metacam 5 mg/mL Solution for Injection on day 1. The dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14. Variables evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Variables assessed by owners included mobility, ability to rise, limping, and overall improvement.

In this field study, dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all variables.

Animal Safety:

Dogs: 3 Day Target Animal Safety Study - In a three day safety study, Metacam 5 mg/mL Solution for Injection was administered intravenously to Beagle dogs at 1, 3, and 5 times the recommended dose (0.2, 0.6 and 1.0 mg/kg) for three consecutive days. Vomiting occurred in 1 of 6 dogs in the 5X group. Fecal occult blood was detected in 3 of 6 dogs in the 5X group. No clinically significant hematologic changes were seen, but serum chemistry changes were observed. Serum alkaline phosphatase (ALP) was significantly increased in one 1X dog and two of the 5X dogs. One dog in the 5X group had a steadily increasing GGT over 4 days, although the values remained within the reference range. Decreases in total protein and albumin occurred in 2 of 6 dogs in the 3X group and 3 of 6 dogs in the 5X group. Increases in blood urea nitrogen (BUN) occurred in 3 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group and 2 of 6 dogs in the 5X group. Increased creatinine occurred in 2 dogs in the 5X group. Increased urine protein excretion was noted in 2 of 6 dogs in the control group, 2 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group, and 5 of 6 dogs in the 5X group. Two dogs in the 5X group developed acute renal failure by Day 4. Bicarbonate levels were at or above normal levels in 1 of the 3X dogs and 2 of the 5X dogs.

Histological examination revealed gastrointestinal lesions ranging from superficial mucosal hemorrhages and congestion to erosions. Mesenteric lymphadenopathy was identified in 2 of 6 dogs in the 1X group, 4 of 6 dogs in the 3X group, and 5 of 6 dogs in the 5X group. Renal changes ranged from dilated medullary and cortical tubules and inflammation of the interstitium, to necrosis of the tip of the papilla in 2 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group, and 4 of 6 dogs in the 5X group.

Injection Site Tolerance - Metacam 5 mg/mL Solution for Injection was administered once subcutaneously to Beagle dogs at the recommended dose of 0.2 mg/kg and was well-tolerated by the dogs. Pain upon injection was observed in one of eight dogs treated with meloxicam. No pain or inflammation was observed post-injection. Long term use of Metacam 5 mg/mL Solution for Injection in dogs has not been evaluated.

Effect on Buccal Mucosal Bleeding Time (BMBT) - Metacam 5 mg/mL Solution for Injection (0.2 mg/kg) and placebo (0.4 mL/kg) were administered as single intravenous injections to 8 female and 16 male Beagle dogs. There was no statistically significant difference ($p > 0.05$) in the average BMBT between the two groups.

Storage Information: Store at controlled room temperature, 68-77°F (20-25°C).

How Supplied:

Metacam 5 mg/mL Solution for Injection: 10 mL vial

Manufactured by:

Boehringer Ingelheim Vetmedica, Inc.
St. Joseph, MO 64506 U.S.A.

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