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.

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, alcohol 15%, glycerol 10%, polysodium 188.5%, sodium chloride 0.6%, melanin, and distilled water 0.3%, in water for injection, pH adjusted with sodium hydroxide and hydrochloric acid.

Indications: Dogs: Melacam (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 Melacam and other treatment options before deciding to use Metacam. Use the lowest effective dose for the shortest duration consistent with individual response.

Dogs: Melacam 5 mg/mL Solution for Injection should be administered initially as a single dose at a dose of 0.09 mg/lb (0.2 mg/kg) body weight intravenously (IV) or subcutaneously (SQ), followed, after 24 hrs, 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 veterinarian if symptoms persist or worsen.

Adverse Reactions:

Gastrointestinal:

- Vomiting, diarrhea, melena, gastrointestinal ulceration
- 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.
- Increased creatinine occurred in 2 dogs in the 5X group. Increased urine 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 and albumin occurred in 2 of 6 dogs in the 3X group and 3 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: Melacam 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 previously diagnosed.

Effect on Buccal Mucosal Bleeding Time (BMBT): - Melacam 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: Melacam 5 mg/mL Solution for Injection: 10 mL vial

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

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For a complete list of adverse reactions for meloxicam reported to the CVM see: \[http://www.fda.gov/vets/VeterinarySafetyHealth/ProductSafetyInformation/cvm/55394.htm\]

In a field study involving 224 dogs was conducted. Based on the results of this study, GI abnormalities were the most common adverse reactions associated with Melacam treatment. Dogs should be observed for signs of potential drug toxicity.

Adverse Reactions Observed During Field Study

<table>
<thead>
<tr>
<th>Clinical Observation</th>
<th>Meloxicam (n=109)</th>
<th>Placebo (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea/Soft Stool</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Inappetence</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Bloody Stool</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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 (1-866-636-2226).

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Consider appropriate washout times when switching from corticosteroid use to meloxicam in cats. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or gastrointestinal peritonitis, repeated use in cats has been associated with acute renal failure and death.

Foreign Experience:
In one study, one cat in each NSAID treatment group had increased intraoperative hemorrhage. NSAID class of analgesic may be necessary. Aspirin, metaproterenol, and acepromazine were used in each group. All cats were premedicated with acepromazine, induced with propofol and maintained on isoflurane. Pain assessment variables evaluated by veterinarians included additional pain intervention therapy, gait/lameness score, analgesia score, sedation score, general impression subjective pain scale, and the visual analog scale score. Additionally, a cumulative pain score, which was the sum of the analgesia, sedation, heart rate and respiratory rate scales was evaluated. A palpebrale was used to quantify the threshold.

Aspirin and butorphanol, which were used in the butorphanol group, both have the potential to add additional analgesic intervention in the 0-24 hour post-surgical period, with the majority of these interventions taking place within the first hour. Therefore, the percentage of cats in each group that received one or more interventions was designated as the primary assessment variable. Approximately half of the cats in each group received a pain intervention as a result of the first (time 0) post-surgical evaluation, i.e., extubation. At this point, the need to provide a pain intervention may be statistically significant between the two groups (p=0.0125). However, the median number of interventions was one per cat in the meloxicam group and two per cat in the butorphanol group and this difference was statistically significant (p=0.0021). The statistical evaluation supports the conclusion that meloxicam test article was better tolerated prior to the butorphanol active control. Forty-eight of the 72 cats in the meloxicam group received one or more interventions (66.7%), and 47 of 66 cats in the butorphanol group received one or more interventions (71.2%). The number of interventions administered to the meloxicam group was less than the butorphanol group at 1, 3, 5, 8, 12, and 24 hours post-surgery.

Cats receiving Metacam 5 mg/mL Solution for Injection showed improvement in the pain assessment variables.

Adverse Reactions:
Cats: A field study involving 138 cats was conducted. Of the 72 cats receiving Metacam 5 mg/mL Solution for Injection in each NSAID treatment group, 3 cats (8.3%) experienced post-treatment elevated serum uroica nitrogen (BUN) levels. The pre-treatment values were in the normal range. Of the 66 cats in the butorphanol treatment group, no cats experienced post-treatment elevated serum uroica nitrogen levels. Nine cats (12.5%) receiving Metacam 5 mg/mL Solution for Injection had post-treatment anemia. Pre-treatment, these cats all had hematocrit and hemoglobin values in the normal range. Four cats (6.1%) in the butorphanol treatment group died. All but one cat had elevated white blood cell count post-treatment (hematocrit<21% and hemoglobin<7.0 g/dL) had normal pre-treatment values. Twenty-four hours after the injection with Metacam 5 mg/mL Solution for Injection, one cat experienced pain upon palpation of the injection site.

Foreign Experience:
Repeated use in cats has been associated with acute renal failure and death. In studies used for the foreign approval of Metacam 5 mg/mL Solution for Injection in cats, lethargy, vomiting, inappetence, and transient pain immediately after injection were noted. Diarrhea and fecal occult blood have also been reported.

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:

1. Gastrointestinal: Vomiting, diarrhea, anorexia
2. Cardiovascular: Hypertension, congestive heart failure
3. Neurologic/Behavioral: Lethargy, depression

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 the Material Safety Data Sheet, or for technical assistance, call 1-866-METAMIC (1-866-638-2266).

For a complete listing of adverse reactions for meloxicam reported to the CVM see: http://www.fda.gov/vets/AdverseDrugEvents/productSafetyInformation/ue0955394.htm

Intramuscular injection of 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 weight loss.

Cat owners should be advised when their pet has received a meloxicam injection. Cat owners should consult their veterinarian immediately if possible adverse reactions are observed.

Clinical Pharmacology:
Meloxicam has nearly 100% bioavailability after subcutaneous injection in cats. The terminal elimination half life after a single dose is estimated to be approximately 15 hours (+/- 10%) in cats. Peak drug concentrations of 1.1 mcg/mL can be expected to occur within 1.5 hours following a 0.3 mg/kg subcutaneous injection in cats. The volume of distribution (Vd) in cats is approximately 0.27 L/kg, with an estimated total systemic clearance of 0.013 L/hr/kg. The drug is 97% bound to plasma proteins.

Effective: The effectiveness of Metacam 5 mg/mL Solution for Injection was demonstrated in a masked field study involving a total of 138 cats representing various breeds. This study used butorphanol as an active control. Cats were either administered a single subcutaneous injection of Metacam 5 mg/mL Solution for Injection or 0.4 mg/kg butorphanol prior to euthanectomy, either alone or in conjunction with other medications for anesthetic or post-operative pain control. All cats were pretreated with acepromazine, induced with propofol and maintained on isoflurane. Pain assessment variables evaluated by veterinarians included additional pain intervention therapy, gait/lameness score, analgesia score, sedation score, general impression subjective pain scale, and the visual analog scale score. Additionally, a cumulative pain score, which was the sum of the analgesia, sedation, heart rate and respiratory rate scales was evaluated. A palpebrale was used to quantify the threshold.

Clinical Safety: A field study involving a total of 138 cats representing various breeds. This study used butorphanol as an active control. Cats were either administered a single subcutaneous injection of Metacam 5 mg/mL Solution for Injection at dosages not to exceed 1.5 mg/kg (5X the recommended dose) resulting in vomiting in three cats (1 of 6 control cats and 2 of 6 cats in SX) and loose stools in four cats (2 of 6 control cats and 2 of 6 cats in SX). Fecal occult blood was detected in ten of the twenty-four cats, one in each control group. This was not a dose-related event. Clinically significant hematologic changes seen included increased PT and APPT in two cats (1 of 6 control cats and 1 of 6 cats in SX). Platelet counts in cats receiving repeated NSAID administration to healthy cats at up to 1.5 mg/kg (5X the recommended dose) resulted in vomiting in three cats (1 of 6 control cats and 2 of 6 cats in SX) and loose stools in four cats (2 of 6 control cats and 2 of 6 cats in SX). Fecal occult blood was detected in ten of the twenty-four cats, one in each control group. This was not a dose-related event. Clinically significant hematologic changes seen included increased PT and APPT in two cats (1 of 6 control cats and 1 of 6 cats in SX). Platelet counts in cats receiving repeated NSAID administration to healthy cats at up to 1.5 mg/kg (5X the recommended dose) resulted in vomiting in three cats (1 of 6 control cats and 2 of 6 cats in SX) and loose stools in four cats (2 of 6 control cats and 2 of 6 cats in SX). Fecal occult blood was detected in ten of the twenty-four cats, one in each control group. This was not a dose-related event. The safety studies demonstrate a narrow margin of safety.

Histological examination revealed gastrointestinal lesions ranging from inflammatory cell infiltration of the mucosa of the GI tract to erosions. Mesenteric lymphadenopathy was identified in 1 of 6 cats in SX. Renal lesions included tubular atrophy, interstitial fibrosis, and chronic inflammation. All cats were premedicated with acepromazine, induced with propofol and maintained on isoflurane. Pain assessment variables evaluated by veterinarians included additional pain intervention therapy, gait/lameness score, analgesia score, sedation score, general impression subjective pain scale, and the visual analog scale score. Additionally, a cumulative pain score, which was the sum of the analgesia, sedation, heart rate and respiratory rate scales was evaluated. A palpebrale was used to quantify the threshold.

Injection Site Tolerance: Histopathology of the injection sites revealed hemorrhage and inflammation, myofiber atrophy, panniculitis, fibrin deposition, and fibroblast proliferation. These findings were present in cats in all groups, with the SX cats having the most present. No repeat dose has been established in cats.

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

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