DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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NADA 141-213

Ms. Beverly D. Crowley
Specialist, Pharmaceutical Regulatory Affairs
Boehringer Ingelheim Vetmedica, Inc.
15th & Oak Streets
P.O. Box 338
Elwood, KS 66024

Dear Ms. Crowley,

The Division of Surveillance (DOS) has reviewed a detailer (MET-3-1003.10), customer brochure (MET-3-1003.11), mini-detailer (MET-3.25) included by Boehringer Ingelheim Vetmedica, Inc. (BIV) in a Drug Experience Report submitted to the Center for Veterinary Medicine (CVM) on June 19, 2003. CVM has also reviewed the direct mailer (MET-3-1003.5B), and an advertisement in *Veterinary Forum* (July 2003) for Metacam® (meloxicam). These materials contain statements that are false or misleading in violation of section 502(a) and (n) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 352(a) and (n), and that encourage use of METACAM in conditions other than those for which CVM has reviewed safety and effectiveness data.

Background

METACAM is indicated for the control of pain and inflammation associated with osteoarthritis in dogs. (62 FR 42967; July 21, 2003 (to be codified at 21 CFR 520.1350).) According to the FDA-approved professional labeling, METACAM is a non-steroidal anti-inflammatory drug (NSAID) for oral use in dogs only. The Precautions section of the labeling includes the following language:

> As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. 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 pre-existing disease that has not been previously diagnosed. Since

> many NSAIDS possess the potential to produce gastrointestinal ulceration, concomitant use of Metacam® Oral Suspension with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored.

Moreover, the labeling discloses several adverse reactions, including gastrointestinal abnormalities, which were the most common adverse reactions associated with the drug in field safety trials:

> Field safety was evaluated in 306 dogs. Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetance) were the most common adverse reactions associated with the administration of meloxicam. During two field studies, certain adverse reactions were observed. Of the dogs that took meloxicam (n=157), forty experienced vomiting, nineteen experienced diarrhea/soft stool, five experienced inappetance, and one each experienced bloody stool, bleeding gums after dental procedure, lethargy/swollen carpus, and epiphora. Of the dogs that took the placebo (n=149), twenty-three experienced vomiting, eleven experienced diarrhea/soft stool, and one experienced inappetance.

Misleading Mechanism of Action Claims

The materials state: "METACAM® is the first NSAID proven in vivo in dogs to be COX-1 sparing/COX-2 inhibiting." They state, further: "COX-1 sparing is demonstrated by not inhibiting PGE_2 (prostaglandin E_2) in the gastric mucosa". These statements are misleading, because they suggest that these attributes are clinically significant, when this has not been demonstrated by substantial evidence or substantial clinical experience. The disclaimer that "clinical relevance has not been shown," appearing in two of the pieces, is presented in a footnote in fine print, and is, therefore, insufficient to correct the overall misleading impression created by the materials.

Misleading Comparative Claims

The materials contain a table reporting the results of a study suggesting that meloxicam is superior to in such areas as "return to normal by day 60" and "owner assessment--significant response at day 30." The materials thus claim that meloxicam is superior to , when this has not been demonstrated by substantial evidence or substantial clinical experience. The study cited to support these statements is not sufficient because of the low number of animals. Moreover, the table is misleading because it highlights one dog in the -treated group that experienced toxic idiosyncratic hepatitis (vomiting, anorexia, lethargy, and jaundice) without disclosing that one dog in the meloxicam treatment group experienced vomiting and was dropped from the study.

Unsubstantiated Safety Claims

The materials state: "Global incidence of reported GI side effects is 0.00013%." This statement implies that, of all animals treated worldwide with METACAM, only 13 in every 100,000 exhibited gastrointestinal side effects. To support this statement, the materials cite "Clinical Expert Statement for renewal of METACAM Oral Suspension for dogs (3/2000-6/2002)." We have not reviewed this document and are not aware of data sufficient to calculate a reliable incidence rate for gastrointestinal side effects. As noted, the PI for METACAM discloses a rate of GI adverse events that is significantly higher than 0.00013 percent.

Lack of Risk Information

With respect to risks associated with METACAM, the materials state that, as with any medication, side effects may occur. The materials state, further, that side effects are usually mild, but may be serious. According to the materials, the most common side effects reported in field studies were vomiting and soft stool/diarrhea. The materials state that dogs should be evaluated for pre-existing medical conditions before treatment, and refer the reader to the package insert for more information.

The materials fail to disclose (as described in the Precautions section of FDA-approved professional labeling) the risks of concurrent administration of NSAIDs and corticosteroids or potentially nephrotoxic drugs. They are, therefore, misleading.

Conclusion and Requested Action

As discussed above, the materials violate section 502(a) and (n) of the FDCA (21 U.S.C. 352(a) and (n)) because they contain misleading mechanism of action, superiority, and safety claims, and because they omit important risk information.

DOS requests that BIV immediately cease the dissemination of promotional materials for METACAM the same as or similar to those described above. Please submit a written response to this letter on or before March 31, 2004, describing your intent to comply with this request, listing all promotional materials for METACAM the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Surveillance, HFV-216, 7500 Standish Place, Rockville, Maryland 20855. In all future correspondence regarding this matter, please refer to the NADA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for METACAM comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

Mohammad I. Sharar, DVM, M.Sc.
Team Leader
Post-Approval Review Team, HFV-216
Division of Surveillance
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