DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 19 2005

RE: NADA 141-213 – Metacam (meloxicam) oral suspension for dogs
NADA 141-219 – Metacam (meloxicam) solution for injection

Donald A. Buss, Director
Regulatory Affairs
Boehringer Ingelheim Vetmedica, Inc.
15th & Oak Streets
P.O. Box 338
Elwood, KS 66024-0338

NOTICE OF VIOLATION

Dear Mr. Buss:

The Division of Surveillance (DOS) has reviewed a compact disk (CD) disseminated to veterinary practitioners by Boehringer Ingelheim Vetmedica, Inc. (BIVI) entitled "Pain How to Understand, Recognize, Treat, Stop." (a.k.a. The Pain H.U.R.T.S. series). This material causes the drug to be misbranded because the material contains statements and graphic representations that are false or misleading under section 502(a) of the Federal Food, Drug, and Cosmetic Act (FFDCA) [21 U.S.C. 352(a)] and because the material does not bear adequate directions for use, as required by 502(f) of the FFDCA [21 U.S.C. 352(f)].

In addition DOS has reviewed a promotional "Veterinary Bulletin" entitled "In Vivo effects of METACAM (meloxicam) and Aspirin on Blood, Gastric Mucosal and Synovial Fluid Prostanoid Synthesis in Dogs." This bulletin was distributed by a BIVI sales representative to a veterinary practitioner without being requested by that practitioner. These materials contain misleading mechanism of action claims that cause the drug to misbranded under sections 502(a) and (f) of the FFDCA. The bulletin highlights the content of the clinical study of the same title (Jones, CJ., et. al., AJVR, 2002) that was disseminated as an attachment to the bulletin. The bulletin states that the study "clearly demonstrates that meloxicam has a COX-2 selective (COX-1 sparing) effect in the dog (*in vivo*)."

Background

Metacam oral suspension and solution for injection are approved in the U.S. *for the control of pain and inflammation associated with osteoarthritis* in DOGS (68 FR 42968, July 21, 2003, codified at 21 CFR 520.1350; and 68 FR 68724, Dec. 10, 2003, codified at 21 CFR 522.1367). The solution for injection received approval on October 28, 2004, for

one-time only dosing in *CATS for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration when administered prior to surgery* (FR 69523, November 30, 2004). According to the FDA-approved professional labeling, Metacam is a non-steroidal anti-inflammatory drug (NSAID) approved for use in dogs and cats only.

Boehringer Ingelheim Vetmedica, Inc. was issued a notice of violation by letter from CVM on February 23, 2004, that objected to misleading mechanism of action claims, misleading comparative claims, unsubstantiated safety claims, and lack of risk information in various items disseminated by the firm to promote the sale of Metacam. The firm's response dated March 25, 2004 indicates that "BIVI takes great care to insure all promotional materials are accurate, balanced, and acceptable to FDA/CVM."

Unsubstantiated Safety and Efficacy Claims

The "Pain H.U.R.T.S" CD is being disseminated to veterinarians by and on behalf of BIVI, and is promotional in context. The cardboard CD mailer has the colors and markings of promotional materials for Metacam, and has the trademark logo for Boehringer Ingelheim. The return address is Boehringer Ingelheim Vetmedica, Inc., 2621 North Belt Highway, St. Joseph, MO 64506-2002. The title "Pain How to Understand, Recognize, Treat, Stop" is embellished with the photographic images of 5 animals - parrot, guinea pig, cat, reptile, and dog. The CD is a promotional "free sample" that contains brief segments from an instructional or "help seeking" piece concerning pain management. In the "Before and After" section of these segments is a case study that promotes use of Metacam for metabolic bone disease in an Eclectus parrot.

Metacam is not approved for use in birds. This CD thus promotes use of Metacam in species and for conditions other than those for which CVM has reviewed safety and effectiveness data. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Metacam is safe and effective for use in birds. The CD is thus false or misleading, which causes the drug to be misbranded under 502(a) of the FFDCA. In addition, the labeling does not bear adequate directions for use as required by 502(f) of the FFDCA.

Misleading Mechanism of Action Claims

A promotional "Veterinary Bulletin" entitled "*In Vivo* effects of METACAM (meloxicam) and Aspirin on Blood, Gastric Mucosal and Synovial Fluid Prostanoid Synthesis in Dogs" was provided to a veterinary practitioner by a BIVI sales representative. The materials contain multiple objectionable claims including but not limited to: "This study clearly demonstrates that meloxicam has a COX-2 selective (COX-1 sparing) effect in the dog (in vivo)..." and "The only NSAID with this powerful combination of data is METACAM." 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 promotional context in which the statements are made suggests that they have clinical significance. In addition, words such as "clearly demonstrates," "patient," and "toxic

effects" convey to a veterinarian that these statements are based on a study that has clinical significance. BIVI is promoting the attached study, in which the authors concluded only that Meloxicam "appears to selectively inhibit COX-2 and spare COX-1," as clinically significant "*in vivo*" evidence that "clearly demonstrates" their product's COX receptor selectivity. Without a disclaimer, such as *"clinical relevance has not been shown,"* in the same part of the promotional piece, these statements are misleading. There is no disclaimer statement accompanying these materials.

Furthermore, although CVM raised this objection in our letter of February 23, 2004, you are evidently persisting in disseminating this misleading information, and promoting the claim of "only" NSAID shown *in vivo* to inhibit COX-2 and spare COX-1 receptors.

Conclusion and Requested Action

As discussed above, the promotional materials render the drug misbranded under section 502(a) and (f) of the FFDCA [21 U.S.C. 352(a) and (f)] because they contain misleading and unsubstantiated safety, efficacy and mechanism of action claims, and lack adequate directions for use.

The Division of Surveillance requests that BIVI 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, within 30 days following your receipt of this letter, 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, 7519 Standish Place, Rockville, Maryland 20855. 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 FFDCA and FDA implementing regulations.

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