DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 23 2003

NADA 141-203

Marne L. Platt, VMD
Regulatory Affairs Manager
Novartis Animal Health US, Inc.
3200 Northline Avenue
Suite 300
Greensboro, NC 27408

Dear Dr. Platt:

We refer to the following DER submissions:

- Your "Dosing Card" submission of September 24, 2002;
- Your "Sales Aid" submission of October 8, 2002;
- Your "Sales Aid on CD" submission of October 17, 2002;
- Your "Direct Mailer" submission of October 23, 2002;
- Your "Trade Ad" submission of October 25, 2002;
- Your "Trade Ad" submission of November 7, 2002.

We conducted our review of these materials after we had prepared the letter dated January 16, 2003, on similar issues. We have also received additional industry complaint letters regarding marketing practices used in promoting the product Deramaxx (deracoxib).

The Division of Surveillance has reviewed these promotional materials and concluded that they contain false or misleading statements in violation of the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations. In addition, the promotional materials contain information that suggests the use of this product for indications that are not provided for in the approved labeling.

Summary of Violations

The following is not necessarily an exhaustive list of these violations. We are continuing to evaluate the materials and may find additional violations of the FDCA and regulations:

- These promotional materials present data from *in vitro* studies (COX-2 selectivity, COX-1 sparing, IC50 Ratio) in a way that suggests clinical significance when no clinical benefit has been established via substantial evidence. Confirmation with regard to this selectivity should be obtained *in vivo* for sponsors to make such definitive label statements. Moreover, *in vitro* comparisons of relative COX-1 and COX-2 activity of different NSAIDs should not be used due to differences in assaying methods. This issue was specifically addressed in a meeting with CVM and Novartis[1] and in the article by Gierse, et al. (1999)[2] that was provided by Novartis:

  > *"For inhibitors that display distinct mechanism of inhibition of COX-1 and COX-2, calculation of a selectivity ratio based upon IC_{50} determinations is not supportable, since there are no underlying kinetic constraints that are common to each isoform. This points to the need for analysis of selectivity in vivo under physiologically relevant conditions."*

- These promotional materials imply or state that Deramaxx is safer and more effective than other non-steroidal anti-inflammatory drugs. Some examples are *"first and only coxib-class drug"*, IC_{50} comparisons that claim to demonstrate *"how different these molecules truly are"*, and *"next generation efficacy"*. The statement *"uniquely targets the COX-2 enzyme"* likewise implies that the drug is superior to other NSAIDs; however, other subclasses of NSAIDs also target the COX-2 enzyme, and your claim does not appear to be supported by substantial evidence or substantial clinical experience. We are particularly concerned because CVM's objection to this claim was thoroughly discussed with Novartis representatives during application review. Representatives of Novartis agreed with CVM's Office of New Animal Drug Evaluation that there would be no mention of a "different class for COX-2 selective NSAIDs and presently approved NSAIDs".[3] As agreed, the acceptable statement should be: deracoxib is a member of the coxib class of NSAIDs.

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[1] Memo of Meeting on July 30, 2001, Re: I-10270 Z0074, Z0075, I-10865 Z0002, Z0003, Z0004.

[2] Gierse, et al., Kinetic basis for selective inhibition of cyclo-ocygenases. Biochem J. 339, 607-614.

[3] Memo to File, I10270 G0078, October 10, 2001; I-10865 G0005, October 10, 2001; Minutes of Teleconference November 19, 2001.

- These promotional materials contain suggestions that the drug is effective for managing induced synovial inflammation at the 1 mg/kg dose. For example, several of the promotional items contain *"Head-to-head with carprofen"* data that compares the efficacy of deracoxib (1 mg/kg) with that of carprofen (2.2 mg/kg) for lameness associated with induced synovial inflammation. Your product is approved at 3-4 mg/kg for post-operative pain. Promotion of the product at 1-2 mg/kg for induced synovial inflammation suggests use of the product for osteoarthritis. At the time of dissemination of these promotional materials, we were not aware of substantial evidence or substantial clinical experience to demonstrate such efficacy. This representation was misleading because it suggests a use that has not been established by substantial evidence or substantial clinical experience.

- The risk information communicated in your promotional materials fails to communicate the full extent of risk associated with NSAID therapy. Currently, your risk statement on the promotional materials reads:

  "As with all drugs, side effects may occur. These are normally mild, but may be serious. In a field study, the most common side effects were gastrointestinal signs or incision leakage. Dogs should be evaluated for preexisting medical conditions before beginning any new medication and monitored during therapy."

  Whereas, the label's precaution section reads:

  "As a class, cyclooxygenase 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."

  The approved prescribing information states that common side effects are vomiting and diarrhea. By not including the term "NSAID" in the first sentence of your risk statement (e.g. "As with all NSAID drugs…"), and not communicating all critical risk information and precautionary measures, the materials suggest that Deramaxx is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Requested Actions

Novartis should immediately cease dissemination of all advertising and labeling materials for Deramaxx, including those disseminated by sales representatives in the field and at professional meetings, which contain the same or similar claims or presentations.

We remind you of the commitment you made when you signed the New Animal Drug Application Form, FDA 356V, that you will promote your product only in accord with the labeling provided in the approved application.

Please inform us of your intentions within 15 days of the receipt of this letter. If you have any questions, you may contact us at (301) 827-6642.

Sincerely yours,

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