



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

INAD 10294 E0003, G0008

JAN 11 1999

Randy C. Lynn, D.V.M., M.S., DACVP
Director of Product Development
Blue Ridge Pharmaceuticals, Inc.
4249-105 Piedmont Parkway
Greensboro, NC 27410

received
1-14-99

Dear Dr. Lynn:

We refer to your submissions dated September 8, 1998 (E0003), and December 4, 1998 (G0008), to your Investigational New Animal Drug (INAD) file for diclofenac 1% suspension. The drug is a nonsteroidal anti-inflammatory proposed for topical use for the management of pain and inflammation in horses.

The E0003 submission contained protocols for a clinical field trial and a target animal safety study for our review.

The G0008 submission contained a request for categorical exclusion from the requirement to prepare an Environmental Assessment (EA). We have completed our review of the submission and agree that a categorical exclusion under 21 CFR 25.33(e) is appropriate for the INAD. We acknowledge that to your knowledge, no extraordinary circumstances exist which may significantly affect the human environment as discussed under 21 CFR 25.21. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Comments concerning Study Number BRP-DEQ-02, "Clinical Field Trial to Evaluate the Safety and Efficacy of Topically Applied 1% Diclofenac Liposomal Suspension for the Relief of Lameness in Horses":

1. In several telephone conversations with Dr. Ellen Buck, most recently on December 3, 1998, we have discussed substantial modifications to the field trial protocol that you are considering. You mentioned that you may employ an approved positive control in lieu of placebo control as currently written.

In studies using an approved positive control, the test article should perform at least as well as the positive control. Please note that if the positive control is more effective than the test article, the study would not be considered as supportive of the test article's effectiveness. Also, it is generally easier to show effectiveness compared to placebo than to show equivalence to a positive control.

Blinding of all personnel involved in evaluation of the product's effectiveness should be maintained in positively controlled studies, as in placebo controlled studies. This may be more difficult if the dosage form of the test article and positive control are not similar.

2. The primary variable of interest to CVM will be the veterinarian's assessment of lameness score. Range of motion and pain on manipulation are not reliable indicators of pain in horses. Most horses, even those with severe lameness, will exhibit no loss of range of motion. Some horses with pronounced loss of range of motion will be perfectly sound. A severe loss of range of motion would generally be 25%. Similarly, many lame horses will not show any signs of pain on passive flexion of the affected joint. Owners' evaluations will not be considered in our analysis of diclofenac's effectiveness.
3. The protocol includes several interim lameness exams. Our effectiveness evaluation will be based on the difference between initial and final lameness evaluations. If improvement is noted only during interim evaluations, it will not be considered evidence of the product's effectiveness.
4. The lameness scoring scale currently proposed is somewhat vague. Instead, we recommend that you use the generally recognized American Association of Equine Practitioners (AAEP) lameness scoring scale.
5. A sample size of 25 horses per group may be too small to detect effects of interest in this protocol. For example, we might expect around 20% of animals in the placebo group to show improvement after 7 days. With 25 horses/group, the underlying percentage improvement of horses in the treatment group would have to be approximately 55% or greater for a statistical test to detect a significant difference. With 50 horses/group, this underlying percentage improvement drops to approximately 45% or greater.
6. Please provide clarification about how data from animals withdrawn from the study due to lack of effectiveness will be evaluated. We recommend that an animal that is withdrawn due to lack of effectiveness be scored as "Did not improve". The number of animals that were withdrawn due to lack of effectiveness can also be compared statistically between the two groups.
7. You have proposed a non-parametric test to compare the two groups. This test is appropriate for tests done cross-sectionally at each time period. However, the test cannot incorporate information about the animal's condition at baseline. We

recommend that the percentage of animals showing improvement by at least one level of the lameness scale between Day 0 and Day 7 be considered primary and be analyzed by an exact test procedure. The animals that were withdrawn due to lack of effectiveness should be included in this analysis.

Comments concerning Study Number BRP-DEQ-04, "Target Animal Safety Study of 1% Diclofenac Liposomal Suspension Applied Topically to Horses – A 28 Day Study";

1. A review of available publications concerning the use of topical diclofenac in humans suggests that the drug is absorbed systemically, and that it is capable of causing adverse reactions typical of many NSAIDs, most notably gastric irritation. Therefore, we recommend modifying the Target Animal Safety study to better identify the occurrence, if any, of systemic adverse reactions that could develop following overdose, such as might occur following overzealous application of the product by a horse owner.

In the protocol as written, all applications of drug will be to a single joint. The advantage of this technique is that it may maximize signs of dermal or local irritation. However, we believe applying portions of the dose to more than one joint, thereby covering more surface area with the drug, may result in increased absorption of diclofenac, and give a better indication of its systemic effects following overdose. In real-life overdose situations, one would anticipate owners both applying excessive amounts of drug to a single joint, and applying drug to multiple joints.

We also recommend including periodic endoscopic evaluation of the stomach, preferably pretreatment and at least once mid study, since this is the only definitive method for diagnosing gastric erosion or ulceration.

2. The protocol states that the study will be conducted for 28 days. The Target Animal Safety Study should be conducted for at least 3X the intended duration of treatment. In our conference on June 30, 1998, you stated your intention to pursue a 14 day treatment duration. For a labeled treatment duration of 14 days, safety studies should be conducted for a minimum of 42 days.
3. The protocol includes 1X, 3X, and 5X multiples of the intended dose. A 10X acute toxicity group should also be evaluated, for at least 1X the intended duration of treatment. You may either include a 10X group in this study, or conduct a separate acute toxicity study. In order to minimize the number of horses sacrificed, you may prefer to incorporate the 10X group into this study, and conduct complete necropsy and histopathologic examination on the 10X group. You should sacrifice and

evaluate all horses in a given treatment group (for example, all 10X horses and all control horses), rather than a limited sample of horses within a treatment group.

Please note that the intent of Target Animal Safety Studies is not only to characterize the types of toxicities that may result from treatment, but also to identify at what dose level any adverse effects begin to manifest. If you elect to sacrifice only the highest treatment dose group, and lesions are found on gross examination or on histopathology, it would be necessary to sacrifice lower dose treatment groups in order to better identify at what dose level toxicity begins. If alterations are not apparent until histopathologic evaluation, and the remaining animals have been off treatment for some time, it may be necessary to repeat the study, at a minimum with the lower dose groups.

4. In addition to the tissue samples to be evaluated outlined in the protocol, a more comprehensive evaluation of the test site should also be conducted. This should include complete histopathology of the joint and related structures (synovium, cartilage, subchondral bone) over which the topical product is applied. A synovial fluid analysis should also be conducted. If all applications are to be made on a single joint, examination of the contralateral untreated joint from the same animal may afford the most meaningful comparison when looking for localized adverse effects.
5. Page 9 of the protocol states "Supplemental feed consumption will be measured and recorded weekly during the study." We are unclear what is meant by "supplemental feed consumption." We agree that feed consumption should be measured, at least at intervals, during the study. Loss of appetite secondary to gastric irritation is a potential adverse reaction to NSAIDs.
6. Blinding of the study should be maintained to reduce the risk of bias in interpreting the results. The frequency of application of diclofenac will make apparent which horses belong to which dosage group. Therefore, the individual(s) making antemortem and postmortem evaluations should not be involved in application of the product, or otherwise be aware of treatment group assignment. The protocol should state how blinding of the study will be maintained.
7. The untreated control horses should receive sham treatment, such as application of saline solution to a specified joint, or massage of the skin over a selected joint, to mimic the handling and manipulation of the treated animals. Such treatment would help identify which lesions that appear on necropsy, if any, are due to handling stress, as opposed to actual treatment effects.

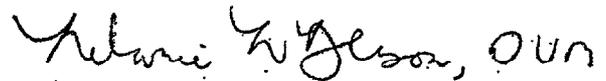
8. To your proposed group pair-wise comparisons and repeated measures ANOVA, we recommend that you add an inspection of the interaction of gender with the other fixed effects. Because the number of animals in each gender by treatment group is small (3), you may want to inspect the interaction of gender with other fixed effects graphically rather than analytically. The decision of whether or not to pool data across gender should be on the basis of this inspection.

Again, because the number of animals in each gender by treatment group is small, you may consider inspecting the model residuals graphically rather than conducting a formal test for heteroscedastic error to motivate the use of variance stabilizing transformations.

Future correspondence regarding these submissions to your INAD file should be identified by the submissions' correspondence date and our file numbers, INAD 10294 E0003, G0008, and submitted directly to the Document Control Unit (HFV-199).

If you have any questions or if we can be of further assistance, please contact Dr. Linda Wilmot, Leader, Equine and Antimicrobial Drugs Team. The telephone number is (301) 827-7540.

Sincerely yours,



Melanie R. Berson, DVM
Director
Division of Therapeutic Drugs
for Non-Food Animals
New Animal Drug Evaluation
Center for Veterinary Medicine