



I-009321-P-0096-EF

MAY 23 2008

U.S. Department of the Interior
Fish and Wildlife Service
Aquatic Animal Drug Approval Partnership Program
Attention: David Erdahl, Ph.D.
Branch Chief, AADAP
4050 Bridger Canyon Road
Bozeman, MT 59715

Re: Effectiveness technical section for chloramine-T

Dear Dr. Erdahl:

Your Effectiveness technical section for the use of chloramine-T to control mortality in largemouth bass due to external columnaris disease is incomplete. In your submission dated November 21, 2007, you submitted to the Investigational New Animal Drug (INAD) file 009321 supporting documentation, raw data, and a final study report (Study Number CHLT-07-EFF.1-02) entitled "The Efficacy of Chloramine-T to Control Mortality of Largemouth Bass *Micropterus salmoides* Caused by External Columnaris, Causative Agent *Flavobacterium columnare*" in support of the Effectiveness technical section for chloramine-T in largemouth bass. You also included draft Freedom of Information (FOI) Summary language. The proposed indication for chloramine-T when administered at a dose of 20 mg/L in a continuous flow water supply or as a static bath for 60 minutes once daily on consecutive days for three treatments is to control mortality in largemouth bass due to external columnaris disease associated with *Flavobacterium columnare*.

We have the following comments:

1. Study CHLT-07-EFF.1-02 contains a deviation that has not been addressed and needs to be described before CVM can accept the study. In Appendix B, Form 10, it states that '200 fish were lost due to jumping, probably caused by light flicker, bumping the tanks, feeders, and feeding'. The form indicates this happened over the first three days (July 14 to July 16) of the study. The final study report does not include this as a deviation nor does it discuss which tanks lost fish. Please describe the events surrounding this deviation, including the definitive numbers of fish lost from each tank, and re-analyze the data. If the specific numbers of fish lost are unknown, please re-analyze the data for worst-case scenarios to ensure that the 200 fish lost did not impact the study results. Please contact the CVM Biometrics Team to discuss the analysis.
2. We noted the expiration date of the test article used during the study was not provided in the final study report (FSR). Please provide this information.

3. The protocol indicates that all dose verification samples will be collected 30 to 45 minutes into the 60-minute bath and will be analyzed within two hours of collecting samples. We note that the time of water sample analysis was not provided. Please provide the times of analysis or confirm the water samples were properly analyzed.

DRAFT LABEL CLAIM LANGUAGE

We appreciate your cooperation by including the relevant portions of the draft label language with this submission. Please submit the effectiveness section of your draft labeling when you resubmit your Effectiveness technical section.

ALL OTHER INFORMATION (AOI)

The AOI submitted is adequate at this time. However, please submit any additional information when you resubmit your Effectiveness technical section.

FOI SUMMARY COMMENTS

We appreciate your cooperation by including the relevant portions of the FOI Summary with this submission. Please resubmit the Effectiveness section of your FOI Summary when you resubmit your Effectiveness technical section. The effectiveness section of the FOI Summary will be reviewed once you provide the requested information and the study results are confirmed.

ADDITIONAL COMMENTS

We offer the following recommendations for future study submissions. We believe that incorporating these recommendations will improve the quality of your submissions.

1. The final study report does not include a report from the Study Monitor. The Study Monitor should have conducted on-site inspections or been in contact with the Investigator to determine whether study procedures were being conducted according to the study protocol. Information about the Study Monitor contacts with the Investigator need to be recorded in the form of a report, and this report included with the raw data. Please refer to Section 5 of Guidance for Industry Number 85 – Good Clinical Practice, available on the CVM website, for future final study reports.
2. We noted that the final disposition of fish used during the study was not provided. We agree that this did not impact the study conclusions, however, please provide this information in future FSR's.
3. Salt and MS-222 are considered drugs and their concurrent use during pivotal studies should be limited. The use of these drugs was reported and we agree that it did not impact the conclusions about the effect of the drug in this study. In future studies, please avoid the use of concurrent medications.

4. In the protocol, it states that water hardness, alkalinity, and pH were to be measured four times during the study. In the future we recommend that these parameters be collected on four different days during the study (i.e. not two on one day and two on another day).
5. The FSR states that "chronic mortality in the reference population was caused by columnaris disease and exacerbated by water quality issues (most notably ammonia and elevated CO₂)." In future submissions please provide the values of any water quality parameter that contribute to morbidity and mortality and discuss the potential impact of on the results.

If you submit correspondence relating to your submission to the investigational file, you should reference the date and the principal submission identifier found at the top of this letter. If you have any questions, please contact me at 240-276-8341 or Dr. Donald Prater, Leader, Aquaculture Drugs Team, at 240-276-8343.

Sincerely,



Cindy L. Burnsteel, DVM
Acting Director, Division of Therapeutic
Drugs for Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine



United States Department of the Interior



U.S. FISH & WILDLIFE SERVICE
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November 21, 2007

Dr. Joan Gotthardt
Director, Division of Therapeutic Drugs
for Food Animals
Document Control Unit, HFV-199
Center for Veterinary Medicine
7500 Standish Place, MPN-2
Rockville, MD 20855

Dear Dr. Gotthardt:

The purpose of this submission is to request 1) a formal review of the enclosed Final Study Report (FSR) titled "The Efficacy of Chloramine-T to Control Mortality in Largemouth Bass *Micropterus salmoides* Caused by External Columnaris, Causative Agent *Flavobacterium columnare*," and 2) that CVM consider the Effectiveness Technical Section complete for the following claim: "Use chloramine-T administered in a flow-through or static water bath at a concentration of 20 mg/L for 60 min/d on three consecutive days to control mortality in largemouth bass *Micropterus salmoides* caused by external columnaris." The FSR is identified by Study Number CHLT-07-EFF.1-02. The study was conducted under Study Protocol CHLT-07-EFF.1.

As per previous CVM guidance, you informed us that to complete the effectiveness technical section data requirements for this type of claim, we were required to provide CVM with the following information:

1. Draft label claim language,
2. Draft language for the dose characterization portion of the effectiveness claim,
3. All other information we are aware of pertaining to the effectiveness of chloramine-T for this claim, and
4. Effectiveness Freedom of Information (FOI) Summaries.

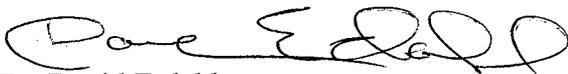
Information with respect to Items 1 – 3 as described above is provided in Attachment 1: All Other Information. The FOI summary is enclosed with the FSR. Please note that we also request that this letter be included in the chloramine-T efficacy technical section in support of a

New Animal Drug Application approval for chloramine-T, and that the letter be filed in the Service's Investigational New Animal Drug (INAD) file #9321. Additional data (Final Study Reports and FOI Summaries) to support the Effectiveness Technical Section complete request for this claim have been previously submitted to CVM (see Study Number CHLT-07-EFF.1-01 submitted to CVM with a letter dated September 25, 2007). We refer to your INAD file number I-9321 E-0086 dated July 26, 2007.

The enclosed FSR, including the FOI Summary, demonstrated that 20 mg/L chloramine-T administered as a static bath for 60 min/d on three consecutive days was effective in controlling mortality caused by external columnaris in fingerling largemouth bass. Although mean cumulative mortality at the end of the 14-d post-treatment period in treated tanks (17.9%) was lower than that in control tanks (21.9%), a significant difference was not detected ($P = 0.4842$). However, mean cumulative mortality was significantly lower in treated tanks than in control tanks on post-treatment days 1 ($P = 0.0005$) and 7 ($P = 0.0063$). Analytical verification of water samples collected during treatments confirmed chloramine-T treatment concentrations were within $\pm 25\%$ of the target concentration. Over the course of the study, test fish were described as hyperactive during the treatment period but exhibited normal behavior during the post-treatment period. Feeding behavior was considered normal throughout the study. The environmental and culture conditions were characterized as adequate for rearing healthy largemouth bass.

The current sponsor of INAD #9321 is Dr. David Erdahl, Branch Chief, Aquatic Animal Drug Approval Partnership (AADAP) Program, U.S. Fish and Wildlife Service, 4050 Bridger Canyon Road, Bozeman, MT. We would like to thank you in advance for your time and consideration with respect to the above-described requests. If you have any questions, please contact Dr. Erdahl at (406) 994-9904.

Sincerely,



Dr. David Erdahl
Branch Chief, AADAP Program

Enclosure: 3 copies of FSR CHLT-07-EFF.1-02 (including the FOI Summary)
1 copy of Study Protocol CHLT-07-EFF.1
3 copies of Attachment 1: All other information relative to the effectiveness of chloramine-T to control mortality caused by external columnaris in largemouth bass

Attachment 1: All other information relative to the effectiveness of chloramine-T to control mortality caused by external columnaris in largemouth bass

1. Draft label claim language:

Use chloramine-T administered in a flow-through or static water bath at a concentration of 20 mg/L for 60 min/d on three consecutive days to control mortality caused by external columnaris in largemouth bass *Micropterus salmoides*.

2. Dose Characterization:

A dose of 20 mg/L administered for three consecutive days for 60 min/d was selected as the therapeutic dose for this label claim because it is generally regarded as the dose that will consistently result in treatment efficacy. The effectiveness of this dose is based on the results from numerous trials conducted under USFWS INAD # 9321 and from pivotal effectiveness trials conducted on largemouth bass and walleye. To our knowledge, there are no manuscripts from refereed, peer-reviewed journals in which largemouth bass or representative warmwater finfish were treated with 20 mg/L chloramine-T for 60 min/d to control mortality caused by external columnaris. However, two final study reports describing the effectiveness of this treatment regimen on walleye have been submitted to CVM in support of a NADA. Below is a list of documents that support the effectiveness of 20 mg/L chloramine-T administered for 60 min/d for three days in flow-through or static water bath treatments on representative cool- and warmwater finfish:

- a. Bowker, J. D. and D. Carty. 2001. Analytical verification of chloramine-T to confirm target dosage in a bath solution administered using a flow-through treatment method. Study Number BFTC-01-CHLT-FT-01. See CVM response INAD# 4000 H-0091 dated June 10, 2002.
- b. Rach J. J. 2003. Efficacy of chloramine-T to control mortality associated with external columnaris on walleye fingerlings (*Stizostedion vitreum*). Study Number CAP-02-CLT-06. See CVM response number 010974 P 0004 dated January 30, 2004.
- c. Altinok, I. 2004. Toxicity and therapeutic effects of chloramine-T for treating *Flavobacterium columnare* infection of goldfish. *Aquaculture* 239:47-56.
- d. Rach, J. J., T. Brady, T. M. Schreier, and D. Aloisi. 2006. Safety of Fish Therapeutants to Glochidia of the Plain Pocketbook Mussel during Encystment on Largemouth Bass. *North American Journal of Aquaculture* 68:348-354.
- e. Bowker, J. D., T. A. Bell, and M. P. Bowman. 2007. The efficacy of chloramine-T to control mortality of walleye *Sander vitreus* caused by columnaris, causative agent *Flavobacterium columnare*. Study Number CHLT-96-EFF-07 submitted to CVM on August 14, 2007 (review pending).
- f. Chloramine-T data on largemouth bass: INAD #9321 data from 2004 – 2007, in which 20 mg/L was administered daily on 2 or 3 days for 60 min/d in nine trials at two different hatcheries. Eight of the nine treatment trials, involving a total of approximately 250,000 fish, were considered efficacious.

- g. Chloramine-T data on cool- and warmwater finfish (other than largemouth bass): INAD #9321 data on cool- and warmwater finfish from 2004 – 2007, in which 20 mg/L was administered daily on 3—6 days for 60 min/d in twenty five trials at four different hatcheries. Seventeen of the twenty five treatment trials, involving a total of approximately 360,000 fish, were considered efficacious.

3. All Other Information:

We know of no additional scientifically valid, statistically defensible studies that have been, or are currently being, conducted in support of this label claim. Please be aware that the USFWS will continue to collect data under INAD #9321 until the time that chloramine-T is approved at this dose for this claim.