

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-059

For the use in combination of:

BMD[®]10, BMD[®]25, BMD[®]30, BMD[®]40, BMD[®]50, BMD[®]60 or
BMD[®]75; and CTC[®]50, CTC[®]65, or CTC[®]70 Type A Medicated Articles

Sponsored by:

ALPHARMA, Inc.
One Executive Drive
Fort Lee, New Jersey 07024

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I. GENERAL INFORMATION

NADA NUMBER: 141-059

SPONSOR: ALPHARMA, Inc.
One Executive Drive
Fort Lee, New Jersey 07024

ACCEPTED DRUG NAME: bacitracin methylene disalicylate
chlortetracycline

TRADE NAME: BMD[®]10, BMD[®]25, BMD[®]30, BMD[®]40,
BMD[®]50, BMD[®]60 or BMD[®]75; and
CTC[®]50, CTC[®]65, or CTC[®] 70

MARKETING STATUS: Over-the-counter

II. INDICATIONS FOR USE

Bacitracin methylene disalicylate Type A Medicated Articles (NADA 46-592): For increased rate of weight gain and improved feed efficiency.

Chlortetracycline Type A Medicated Articles (NADA 46-699): For treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis*, and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline.

III. DOSAGE

Dosage Form: This NADA provides for the combined use of two Type A Medicated Articles, bacitracin methylene disalicylate as per 21 CFR 558.76 and chlortetracycline as per 21 CFR 558.128 (a)(3). Bacitracin methylene disalicylate is supplied as a Type A Medicated Article in concentrations of 10, 25, 30, 40, 50, 60, or 75 grams of bacitracin activity per pound. Chlortetracycline is supplied as a Type A Medicated Article in concentrations of 50, 65, or 70 grams, chlortetracycline per pound.

Route of Administration: Oral, in feed.

Recommended Dosage: In Type C Medicated Feed, 10 to 30 grams bacitracin methylene disalicylate per ton and approximately 400 grams chlortetracycline per ton, varying with body weight and feed consumption to provide 10 mg/lb body weight daily. Feed for not more than 14 days.

IV. EFFECTIVENESS

A. EFFECTIVENESS OF COMPONENT PREMIXES

The approved original NADA 46-592 for BMD® (bacitracin methylene disalicylate) Premixes contained data to establish that this product was effective for increased rate of weight gain and improved feed efficiency in swine when feed continuously at 10 to 30 g/ton of feed (30 FR 15845).

Indications for chlortetracycline premixes accepted through the Drug Efficacy Study Implementation (DESI) of findings of the National Academy of Science and National Research Council (NAS/NRC) include use in swine feed at 400 g/ton (10 mg per pound body weight daily) for the treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* and treatment of bacterial pneumonia caused by *Pasteurella multocida* when fed for 14 days (61 FR 35949).

B. BLOOD LEVEL NONINTERFERENCE STUDY

This new animal drug application for the concurrent use of BMD® and CTC® in swine feed contains data from an adequate and well-controlled study demonstrating the effectiveness of this combination for the indicated claims at the specified dosage.

1. Study type: Noninterference (bioequivalence).
 - a. Purpose: This study was conducted to determine whether BMD administered orally at a subtherapeutic dose would interfere with the absorption or elimination of CTC, also administered orally, when the two drugs were administered concurrently.
 - b. Study Director: Martha A. Ferris, D.V.M., M.S.
Colorado Animal Research Enterprises
6200 E. County Road 56
Fort Collins, Colorado 80524
 - c. General Design
 - 1) Experimental Animals: Ten crossbred commercial-type swine (5 barrows and 5 gilts) weighing initially 16 to 18 kilograms and approximately 7 weeks of age.
 - 2) Dosage Form: Equivalent of Type C medicated feed containing 30 grams BMD per ton and 400 grams CTC per ton
 - 3) Experimental Design: In this two-period crossover study, pigs were dosed by gavage once daily for 7 days with either CTC alone (22.0 mg CTC/kg body weight per day as water soluble CTC; n=12 pigs) or CTC in combination with BMD (22.0 mg CTC /kg body weight per day as water soluble CTC PLUS 1.65 mg BMD/kg body weight per day as water soluble BMD; n=12 pigs). These doses are equivalent to 400 g CTC/ton feed without and with 30 g

BMD/ton feed. Blood samples were taken at various times for up to 30 hours following the seventh day's dosing. Samples were analyzed by microbiological assay for CTC concentration. After a 5-day period without dosing, each pig was given the other treatment for 7 consecutive days. Again, blood was sampled on the seventh day.

- d. Results: The response to treatment, by group, is summarized in Table 4.1.

Table 4.1. Two-period crossover study to determine whether BMD administered orally at a subtherapeutic dose would interfere with the absorption or elimination of CTC

Parameter	Treatment					
	CTC			BMD+CTC		
	Lower limit (80% of mean)	Mean	Upper limit (120% of mean)	Lower limit of 90% Confidence Interval	Mean	Upper limit o 90% Confidence Interval
Area under the curve, &g-h/mL	12.2	15.3	18.3	14	15.8	17.7
C_{max} , &g/mL	1.1	1.37	1.64	1.09	1.38	1.48
T_{max} , hours	2.2	2.8	3.3	2.5	3.6	4.7
k_{el} , hours ⁻¹ (24 to 30 hours)	-0.117	-0.098	-0.078	-0.113	-0.103	-0.092

2. Statistical analysis: For the variables AUC and C_{max} , non-interference was determined by whether the CTC + BMD treatment was within 80% to 120% of the mean for the CTC treatment. T_{max} was considered of secondary significance to AUC and C_{max} .
3. Conclusions: Non-interference was demonstrated for the primary pharmacokinetic endpoints, AUC and C_{max} . In addition, mean values of a secondary endpoint, T_{max} , did not differ ($P > .35$). These results support that CTC's effectiveness is not compromised in the presence of BMD (i.e., bioavailability and maximal serum CTC concentrations were identical).

C. Supportive Efficacy Studies: None.

V. ANIMAL SAFETY

The approved NADA 46-592 for bacitracin methylene disalicylate in feed and NADA 46-699 for chlortetracycline in feed contained adequate data to establish the safety of each drug for swine. The NAS/NRC/DESI conclusions on chlortetracycline in feed for swine indicate that safety as well as effectiveness of this level of use for swine is accepted (61 FR 35949).

The safety of the two drugs when fed together at the proposed levels to swine was demonstrated in a blood level noninterference study of activity and also in the residue depletion study described in this document.

Based on these studies, it is concluded that the combination is safe to be fed to swine.

VI. HUMAN SAFETY

A. Approved NADAs Withdrawal Times

The approved NADA 46-592 for BMD Type A medicated articles contains adequate information establishing it as a zero withdrawal drug at the proposed use level of 10 to 30 g/ton in swine.

The approved NADA 46-699 for CTC Type A medicated articles contains adequate information establishing it as a zero withdrawal drug at the proposed use level of 400 g/ton in swine.

B. Residue Noninterference

The blood level study described in the Effectiveness section of this document showed, that BMD did not alter the elimination of CTC, thereby addressing the residue depletion noninterference of BMD on CTC.

The following study was pivotal in confirming noninterference of CTC on the depletion of BMD for the combination of BMD and CTC in a Type C drug product swine feed.

1. Study type: Tissue residue of bacitracin in swine muscle.
 - a. Purpose: This adequate and well-controlled study was conducted to determine if pigs treated concurrently with CTC and BMD in the feed for 14 days have bacitracin in their tissues exceeding their respective established tissue tolerances.
 - b. Study Director: Martha A. Ferris, D.V.M., M.S.
Colorado Animal Research Enterprises
6200 E. County Road 56
Fort Collins, Colorado 80524
 - c. General Design

- 1) Experimental Animals: The study consisted of crossbred commercial-type swine (5 barrows and 5 gilts) weighing initially 16 to 18 kilograms and approximately 7 weeks of age.
 - 2) Dosage Form: Type C Medicated Feed containing 30 grams BMD per ton and 400 grams CTC per ton
 - 3) Experimental Design: Following a 7-day acclimation period, pigs were assigned randomly to treatment (and pen), relocated to the pen, and the following treatments commenced on Day 1: Control pigs received feed containing no BMD or CTC for 14 consecutive days (1 gilt and 1 barrow housed together) while BMD and CTC pigs received feed containing 30 grams BMD activity per ton and 400 grams CTC activity per ton for 14 consecutive days (2 pens of 2 gilts/pen and 2 pens of 2 barrows/pen). From Day 1 through the evening of Day 14, feeds were offered to allow for *ad libitum* intake. After weighing on Day 15, euthanasia was effected and tissues were collected and processed on an individual animal basis. Bacitracin in muscle was quantified by microbiological assay. The established tolerance for residues of bacitracin in swine muscle at zero withdrawal is 0.02 U/g.
- d. Results: When evaluating noninterference of the assay using the standard test organism *Micrococcus luteus* ATCC 10240, the average recovery of bacitracin was unusually high in tissues spiked with both bacitracin and chlortetracycline. This effect appeared to be due to interference caused by the presence of CTC. However, CTC was shown subsequently not to interfere with a second strain, *M. luteus* Strain EN5.
- Bacitracin residue was not above its established tolerance in any tissue sample assayed using either *M. luteus* ATCC #10240 or Strain EN5.
2. Conclusions: At a zero-day withdrawal, the established tolerance of bacitracin residues in swine muscle is not exceeded in swine fed a ration containing BMD at 30 g/ton and CTC at 400 g/ton for 14 days.

VII. AGENCY CONCLUSIONS

The approved NADA 46-592 for bacitracin methylene disalicylate in feed and NADA 46-699 for chlortetracycline in feed contain adequate data to establish the safety and effectiveness of each drug for swine. The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and Part 514 of the implementing regulations for use in combination. The data demonstrate that the bacitracin methylene disalicylate Type A medicated articles (BMD[®]) and approved chlortetracycline Type A medicated articles, when combined to produce a finished Type C combination medicated feed and when fed to swine under its labeled conditions of use, are safe and effective.

This NADA contains data from an adequate and well-controlled study demonstrating that the tissue concentrations of bacitracin residues are below the established tolerance at a

zero-day withdrawal when feed containing BMD (30 g/ton) and CTC (400 g/ton) was fed as the sole ration for 14 days. In addition, the study described in the Effectiveness section demonstrated that BMD does not alter the elimination of CTC as documented by the lack of effect on the postdosing endpoints. Therefore, human food safety standards have been met for the combination of BMD at 30 g/ton and CTC at 400 g/ton when these two animal drugs are offered as the sole ration for 14 consecutive days. The data support a pre-slaughter withdrawal period of zero days for this drug combination.

NADA 46-592 for bacitracin methylene disalicylate in feed and NADA 46-699 for chlortetracycline in feed were approved as over-the-counter products and this marketing status remains unchanged. Chlortetracycline Type A Medicated Articles in combination with other over-the-counter antibiotics for use in food-producing animals are currently on the market. Therefore, the Center for Veterinary Medicine has concluded that this combination-use product should be granted over-the-counter status.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action is categorically excluded under 21 CFR 25.24(d)(1)(ii) from the requirement to prepare an environmental assessment (EA). The categorical exclusion applies to this action because bacitracin methylene disalicylate and chlortetracycline will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect. The data available to the Agency do not establish that, at the expected exposure level, the substance may be toxic to organisms in the environment.

Under Section 512(c)(2)(F)(ii) of the FFDCA, this approval for food-producing animals does not qualify for marketing exclusivity because the application contains no new clinical or field investigations (other than bioequivalence or residue studies) essential to the approval of the application and conducted or sponsored by the applicant.

VIII. APPROVED PRODUCT LABELING

Copies of the draft facsimile labeling are attached to this document:

CTC/BMD[®] TYPE C MEDICATED FEED BLUEBIRD Label