Date of Approval: June 18, 2020

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-535

Aureo S 700® and Bovatec®

(chlortetracycline, sulfamethazine Type A medicated article) and (lasalocid Type A medicated article)

Type A medicated articles to be used in the manufacture of Type B and Type C medicated feeds

Beef steers and heifers fed in confinement for slaughter; and beef cattle up to 800 lbs.

Original approval of an Animal Drug Availability Act of 1996 (ADAA) feed combination for the indications listed in Section I.L.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-535

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Names

Aureo S 700® and Bovatec®

D. Drug Product Established Names

chlortetracycline, sulfamethazine Type A medicated article and lasalocid Type A medicated article

E. Pharmacological Categories

Aureo S 700®: antimicrobial
Bovatec®: anticoccidial

F. Dosage Form

Type A medicated articles to be used in the manufacture of Type B and Type C medicated feeds

G. Amount of Active Ingredients in Currently Marketed Products[1]

Aureo S 700®: 35 g/lb of chlortetracycline calcium complex equivalent to chlortetracycline HCl and 7.7% (35 g/lb) sulfamethazine (1:1 ratio)[2]
Bovatec®: 90.7 g/lb (20%) of lasalocid (as lasalocid sodium activity)

H. How Supplied

Aureo S 700®: 50 lb bag
Bovatec®: 50 lb bag

I. Dispensing Status

Veterinary feed directive (VFD)

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[1] The sponsors of these individual currently marketed Type A medicated articles may have approvals for other strengths that are for use in the same species and class, for the same indications, and at the same dosages, but are not currently marketing those strengths of these Type A medicated articles. Such strengths, when legally marketed, are also approved for use in the manufacture of Type B and Type C medicated feeds that are the subject of this approval.

[2] Chlortetracycline and sulfamethazine may only be sourced from Aureo S 700®, NADA 035-805, which provides these two drugs at a 1:1 ratio.

J. Route of Administration

Oral

K. Species/Classes

Beef steers and heifers fed in confinement for slaughter; and beef cattle up to 800 lbs.

L. Indications and Dosage Regimens

1. As an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever, and for improved feed efficiency in beef steers and heifers fed in confinement for slaughter.

    a. 35 to 105 g/ton to provide 350 mg per head per day each of chlortetracycline and sulfamethazine (as Aureo S 700®) for use as an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever

    b. 10 to 30 g/ton to provide 100 to 300 mg per head per day of lasalocid (as Bovatec®) for improved feed efficiency

    Feed continuously for 28 days.

2. As an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever, and for improved feed efficiency and increased rate of weight gain in beef steers and heifers fed in confinement for slaughter.

    a. 35 to 42.2 g/ton to provide 350 mg per head per day each of chlortetracycline and sulfamethazine (as Aureo S 700®) for use as an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever

    b. 25 to 30 g/ton to provide 250 to 300 mg per head per day of lasalocid (as Bovatec®) for improved feed efficiency and increased rate of weight gain

    Feed continuously for 28 days.

3. As an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever, and for control of coccidiosis caused by *Eimeria bovis* and *E. zuernii* in beef cattle up to 800 lbs.

    a. 35 to 700 g/ton to provide 350 mg per head per day each of chlortetracycline and sulfamethazine (as Aureo S 700®) for use as an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever

    b. 30 to 181.8 g/ton to provide 1 mg per 2.2 lb body weight per day up to a maximum of 360 mg per head per day of lasalocid (as Bovatec®) for control of coccidiosis caused by *Eimeria bovis* and *E. zuernii*

    Hand feed continuously for 28 days.

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the ADAA of 1996, allows for drugs to be fed in combination in or on medicated feed without additional demonstration of their effectiveness or target animal safety when certain conditions are met. In those cases, the FD&C Act provides that effectiveness and target animal safety of each drug, demonstrated in its NADA at the time of the approval, are adequate. The Agency has based its determination of the effectiveness and target animal safety of the combination of chlortetracycline, sulfamethazine Type A medicated article and lasalocid Type A medicated article on the effectiveness and target animal safety of the previously separately approved conditions of use for Aureo S 700® and Bovatec® for use in beef steers and heifers fed in confinement for slaughter; and beef cattle up to 800 lbs, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness;
- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population;
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness;
- there was not a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that was not adequately evaluated based on the information contained in the application for the combination, and no data presented in the application raised a safety concern with the Agency; and
- there was not a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and no data presented in the application raised a safety concern with the Agency.

The combination of Aureo S 700® and Bovatec® qualifies as a combination meeting the requirements of the FD&C Act, as amended by the ADAA of 1996, listed above. The original approval of NADA 035-805 for Aureo S 700®, a fixed-ratio combination of chlortetracycline and sulfamethazine, contained studies and information to support that each of the active ingredients made a contribution to the labeled effectiveness of Aureo S 700®. The indication for Aureo S 700® "As an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever", is considered an approved therapeutic use because weight losses are commonly experienced in beef cattle with untreated respiratory disease, and the administration of Aureo S 700® will support maintenance of weight during the disease state. The therapeutic use of Aureo S 700® and Bovatec® is limited to beef steers and heifers fed in confinement for slaughter and beef cattle up to 800 lbs with respiratory disease such as shipping fever and requires a VFD with professional veterinary involvement to continue to assure judicious use. The information in NADA 035-805 for Aureo S 700® and NADA 096-298 for Bovatec® satisfied all of the requirements listed above for the ADAA of 1996.

Effectiveness and target animal safety of the individual drugs in this combination has been established by data in the following NADAs (refer to Table II.1):

Table II.1. Summary of effectiveness and target animal safety for the individual drugs subject to this combination.

Drug Product	Indications	Approval Information
Aureo S 700® Sponsored by Zoetis Inc.	For use in feeds for beef cattle as an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever.	NADA 035-805 (as published in the FEDERAL REGISTER (33 FR 15113) on October 10, 1968)
Bovatec® Sponsored by Zoetis Inc.	1. For use in feeds for cattle* fed in confinement for slaughter for improved feed efficiency.[a] 2. For use in feeds for cattle* fed in confinement for slaughter for improved feed efficiency and increased rate of weight gain.[a] 3. For use in feeds for cattle up to 800 lbs for control of coccidiosis caused by *Eimeria bovis* and *E. zuernii*.[b]	NADA 096-298 [a] (refer to the FOI Summary, dated August 6, 1982) [b] (as published in the FEDERAL REGISTER (52 FR 41988) on November 2, 1987)

* The target animal approved in the 1982 approval for Bovatec® is "cattle fed in confinement for slaughter"; this target animal was revised to "beef steers and heifers fed in confinement for slaughter" in the current approval for consistency with the target animal class in the original study data and current target animal class terminology, as described in Guidance for Industry #191, Appendix III.

III. HUMAN FOOD SAFETY

The human food safety of each drug was adequately demonstrated in its NADA at the time of the approval. In general, this means that additional microbial food safety and toxicology data were not needed; however, additional residue chemistry data were needed for residue depletion and assay noninterference for the combination, described below in Section C. The Agency has based its determination of the human food safety of the combination of sulfamethazine, chlortetracycline, and lasalocid on the human food safety of the previously separately approved conditions of use for Aureo S 700® and Bovatec® for use in beef cattle, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, and
- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Microbial Food Safety

With respect to the human food safety evaluation for these types of combination new animal drug approvals, the Agency evaluates whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs of the combination interferes with the methods of analysis of another active ingredient or drug in the combination [section 512(d)(4)(A) of the FD&C Act]. Therefore, the effects of this combination of Aureo S 700® and Bovatec® on antimicrobial resistance development among bacteria of public health concern in or on treated beef cattle was not assessed.

B. Toxicology

Safety of the individual drugs in this combination has been established by data in the following NADAs (refer to Table III.1):

Table III.1. Toxicology assessment of the individual drugs in this combination.

Drug Product	Approval Information
Aureo S 700®	NADA 035-805 (as published in the FEDERAL REGISTER (33 FR 15113) on October 10, 1968)
Bovatec®	NADA 096-298 (refer to the FOI Summary, dated August 6, 1982)

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

CVM did not require residue chemistry studies for this approval. Additional data for residue depletion and assay noninterference from existing approvals were reviewed to support the combination of chlortetracycline and sulfamethazine with lasalocid. Data demonstrating residue depletion in cattle for combinations of chlortetracycline with lasalocid (NADA 141-250), and chlortetracycline with sulfamethazine (NADA 035-805) have previously been

provided. Lasalocid also has been approved for use in cattle alone (NADA 096-298), and in several feed combination products (NADAs 138-992, 138-904, 139-876, 140-288, and 140-579). Residue depletion studies for all lasalocid products in cattle have demonstrated that residues of lasalocid were below the tolerance in cattle liver after a 0-day withdrawal period. We conclude that residues of lasalocid will not exceed the tolerance at the 7-day withdrawal period when combined with chlortetracycline and sulfamethazine. Data provided for the original approval of NADA 035-805 demonstrated that residues of sulfamethazine were below the limits of detection of the assay used (<0.1 ppm) by 2-days withdrawal. Residues of chlortetracycline had depleted to below 0.1 ppm in cattle kidney by the 7-day withdrawal period. We conclude that residues of sulfamethazine and chlortetracycline will not exceed their tolerances in cattle tissues after a 7-day withdrawal period.

2. Target Tissues and Marker Residues

   A target tissue and marker residue were not assigned for chlortetracycline or sulfamethazine in the approval under NADA 035-805 (as published in the FEDERAL REGISTER (33 FR 15113) on October 10, 1968).

   Liver was assigned as the target tissue, and parent lasalocid was assigned as the marker residue in the approval of NADA 096-298 (FOI Summary dated August 6, 1982).

3. Tolerances

   Tolerances for chlortetracycline in edible tissues of cattle are 2 ppm in muscle, 6 ppm in liver, and 12 ppm in fat and kidney (21 CFR 556.150 *per* Federal Register, vol. 61, No. 247, p 67453).

   A tolerance of 0.1 ppm is established for negligible residues of sulfamethazine in edible tissues of cattle (21 CFR 556.670 *per* Federal Register vol. 47, No. 113, p 25323).

   A tolerance of 0.7 ppm is established for lasalocid in cattle liver (21 CFR 556.347 *per* Federal Register vol. 66, No. 75, p 19854).

4. Withdrawal Period and/or Milk Discard Time, and/or Honey Discard Time

   The longest withdrawal period assigned to any of the components of the combination is the 7-day withdrawal period assigned to Aureo S 700® (NADA 035-805). A 7-day withdrawal period is assigned for cattle fed chlortetracycline up to 350 mg/head/day, sulfamethazine up to 350 mg/head/day, and lasalocid up to 360 mg/head/day.

D. Analytical Method for Residues

1. Chlortetracycline

   The analytical method for detection of chlortetracycline residues in tissues is a microbiological assay using *Bacillus cereus* var. *mycoides* (ATCC 11778) as the test organism (Antibiotic Residues in Milk, Dairy Products, and Animal Tissues:

Methods, Reports, and Protocols, Food and Drug Administration, Washington, D.C., 1968).

2. Sulfamethazine

   The analytical method for detection of sulfamethazine residues in cattle tissues is a colorimetric method. The assay uses Bratton-Marshall method to form a colored product followed by detection at 545 nm.

3. Lasalocid

   The HPLC fluorescence detection analytical method for determination of lasalocid sodium residues in cattle liver is described in NADA 096-298 (FOI Summary dated February 20, 2001).

4. Availability of Methods

   The validated analytical methods for analysis of residues of chlortetracycline, sulfamethazine and lasalocid are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical methods, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

IV. USER SAFETY

CVM did not require user safety studies for this approval.

The combination labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type B and Type C medicated feed:

Not for use in humans. Keep out of reach of children.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the FD&C Act and 21 CFR part 514. The data contained in the previously approved NADAs for Aureo S 700® and Bovatec® demonstrate that, when they are used according to the label, they are safe and effective for use 1) as an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever, and for improved feed efficiency in beef steers and heifers fed in confinement for slaughter; 2) as an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever, and for improved feed efficiency and increased rate of weight gain in beef steers and heifers fed in confinement for slaughter; 3) and as an aid in the maintenance of weight gains in the presence of respiratory disease such as shipping fever, and for control of coccidiosis caused by *Eimeria bovis* and *E. zuernii* in beef cattle up to 800 lbs. Additionally, data demonstrate that residues in food products derived from beef cattle administered Aureo S 700® and Bovatec® will not represent a public health concern when the combination medicated feed is used according to the label.

A. Marketing Status

A valid VFD is required to dispense this drug. Any animal feed bearing or containing this drug will be fed to animals only by or on a lawful veterinary feed directive issued by a licensed veterinarian in the course of their professional practice. In addition, the veterinary feed directives issued for this drug are not refillable.

The decision to restrict this drug to use by or upon a lawful veterinary feed directive issued by a licensed veterinarian was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, and because restricting this drug product to use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product and to slow any potential for the development of bacterial resistance to antimicrobial drugs.

B. Exclusivity

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.