Date of Approval: July 28, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-564

Pennchlor® and Rumensin™

(chlortetracycline Type A medicated article) and (monensin Type A medicated article)

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

Beef calves 2 months of age and older, and growing beef steers and heifers fed in confinement for slaughter

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

Sponsored by:

Pharmgate Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-564

B. Sponsor

Pharmgate Inc.
1800 Sir Tyler Dr.
Wilmington, NC 28405

Drug Labeler Code: 069254

C. Proprietary Names

Pennchlor® and Rumensin™

D. Drug Product Established Names

chlortetracycline Type A medicated article and monensin Type A medicated article

E. Pharmacological Categories

Pennchlor®: antimicrobial
Rumensin™: 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]

Pennchlor®: 50, 90 and 100 g/lb of chlortetracycline as chlortetracycline calcium complex equivalent to chlortetracycline hydrochloride
Rumensin™: 90.7 g/lb of monensin, USP

H. How Supplied

Pennchlor®: 22.68 kg (50 lb) bags
Rumensin™: 25 kg (55.12 lb) bags, and 600 kg (1322.77 lb) and 900 kg (1984.16 lb) totes

I. Dispensing Status

Veterinary feed directive (VFD)

[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.

J. Route of Administration

Oral

K. Species/Classes

Beef calves 2 months of age and older, and growing beef steers and heifers fed in confinement for slaughter

L. Indications and Dosage Regimens

1. For treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in beef calves 2 months of age and older.

    a. 10 mg/lb body weight/day of chlortetracycline (as Pennchlor®) for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline.

    b. 0.14 to 1.00 mg/lb body weight/day of monensin (as Rumensin™) to provide, depending upon severity of coccidiosis challenge, up to 200 mg/head/day of monensin for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

    Feed as the sole ration for not more than 5 days, then continue to feed monensin Type C medicated feed alone.

2. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter over 700 lbs.

    a. 0.5 mg/lb body weight/day of chlortetracycline (as Pennchlor®) for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline.

    b. 0.14 to 0.42 mg/lb body weight/day of monensin (as Rumensin™) to provide, depending upon severity of coccidiosis challenge, up to 480 mg/head/day of monensin for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

    Feed as the sole ration.

3. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter over 700 lbs.

    a. 0.5 mg/lb body weight/day of chlortetracycline (as Pennchlor®) for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline.

b. 50 to 480 mg/head/day of monensin (as Rumensin™) for improved feed efficiency.

Feed as the sole ration. No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 grams/ton (360 mg monensin per head per day).

4. For treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter.

   a. 10 mg/lb body weight/day of chlortetracycline (as Pennchlor®) for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline.

   b. 0.14 to 0.42 mg/lb body weight/day of monensin (as Rumensin™) to provide, depending upon severity of the coccidiosis challenge, up to 480 mg/head/day of monensin for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

   Feed as the sole ration for not more than 5 days, then continue to feed monensin Type C medicated feed alone.

5. For treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter.

   a. 10 mg/lb body weight/day of chlortetracycline (as Pennchlor®) for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline.

   b. 50 to 480 mg/head/day of monensin (as Rumensin™) for improved feed efficiency.

   Feed as the sole ration for not more than 5 days, then continue feeding monensin Type C medicated feed alone. No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 grams/ton (360 mg monensin per head per day).

6. For the reduction of the incidence of liver abscesses and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter over 400 lbs.

   a. 70 mg/head/day of chlortetracycline (as Pennchlor®) for the reduction of the incidence of liver abscesses.

b. 0.14 to 0.42 mg/lb body weight/day of monensin (as Rumensin™) to provide, depending upon severity of coccidiosis challenge, up to 480 mg/head/day of monensin for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

Feed as the sole ration.

7. For the reduction of the incidence of liver abscesses and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter over 400 lbs.

   a. 70 mg/head/day of chlortetracycline (as Pennchlor®) for the reduction of the incidence of liver abscesses.

   b. 50 to 480 mg/head/day of monensin (as Rumensin™) for improved feed efficiency.

   Feed as the sole ration. No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 grams/ton (360 mg monensin per head per day).

8. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter under 700 lbs.

   a. 350 mg/head/day of chlortetracycline (as Pennchlor®) for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline.

   b. 0.14 to 0.42 mg/lb body weight/day of monensin (as Rumensin™) to provide, depending upon severity of coccidiosis challenge, up to 480 mg/head/day of monensin for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

   Feed as the sole ration.

9. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter under 700 lbs.

   a. 350 mg/head/day of chlortetracycline (as Pennchlor®) for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline.

   b. 50 to 480 mg/head/day of monensin (as Rumensin™) for improved feed efficiency.

Feed as the sole ration. No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 grams/ton (360 mg monensin per head per day).

10. For the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter.

    a. 350 mg/head/day of chlortetracycline (as Pennchlor®) for the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline.

    b. 0.14 to 0.42 mg/lb body weight/day of monensin (as Rumensin™) to provide, depending upon severity of coccidiosis challenge, up to 480 mg/head/day of monensin for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

    Feed as the sole ration.

11. For the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter.

    a. 350 mg/head/day of chlortetracycline (as Pennchlor®) for the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline.

    b. 50 to 480 mg/head/day of monensin (as Rumensin™) for improved feed efficiency.

    Feed as the sole ration. No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 grams/ton (360 mg monensin per head per day).

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 Type A medicated article and monensin Type A medicated article on the effectiveness and target animal safety of the previously separately approved conditions of use for Pennchlor® and Rumensin™ for use in beef calves 2 months of age and older, and in growing beef steers and heifers fed in confinement for slaughter, 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.

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
Pennchlor® Sponsored by Pharmgate Inc.	1. For use in feeds for calves, beef, and non-lactating dairy cattle for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline. 2. For use in feeds for beef cattle under 700 lbs for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline. 3. For use in feeds for beef cattle over 700 lbs for control of active infection of anaplasmosis caused by *Anaplasma marginale*	NADA 138-935 (refer to the FOI Summary, dated February 16, 1996)

Drug Product	Indications	Approval Information
	susceptible to chlortetracycline 4. For use in feeds for growing cattle over 400 lbs for reduction of liver condemnation due to liver abscesses. 5. For use in feeds for beef cattle for the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline.	
Rumensin™ Sponsored by Elanco US Inc.	1. For use in feeds for calves (excluding veal calves) for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*. 2. For use in feeds for growing beef steers and heifers fed in confinement for slaughter for improved feed efficiency and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*.	NADA 095-735 (refer to 21 CFR 558.355)*

*Elanco US Inc. has provided Pharmgate Inc. right of reference to use Rumensin™ in this combination.

III. HUMAN 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, only additional residue chemistry data and assay noninterference information were needed to support approval of this ADAA feed-use combination. The Agency has based its determination of the human food safety of the combination of chlortetracycline and monensin on the human food safety of the previously separately approved conditions of use for Pennchlor® and Rumensin™ for use in beef calves 2 months of age and older, and in growing beef steers and heifers fed in confinement for slaughter, 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

As noted, Section 512(d)(4)(A) of the FD&C Act, limits CVM's human food safety evaluation for these types of ADAA feed-use combination new animal drug approvals; therefore, microbial food safety was not assessed.

B. Toxicology

As noted, Section 512 (d)(4)(A) of the FD&C Act limits CVM's human food safety evaluation for these types of ADAA feed-use combination new animal drug approvals; therefore, toxicology assessment of these types of combination new animal drugs was not performed. 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
Pennchlor®	NADA 138-935 (as published in the FEDERAL REGISTER (35 FR 11647) on July 21, 1970, and the FOI Summary, dated February 16, 1996)
Rumensin™	NADA 095-735 (refer to the FOI Summary, dated December 16, 1998)

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Study

      CVM did not require total residue and metabolism studies for this approval. NADA 138-935 contains summaries of information supporting the approval of chlortetracycline in cattle (35 FR 11647, dated July 21, 1970). NADA 095-735 contains summaries of information supporting the approval of monensin in cattle (40 FR 58289, dated December 16, 1975).

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval. NADA 138-935 contains summaries of information supporting the approval of chlortetracycline in cattle (35 FR 11647, dated July 21, 1970). NADA 095-735 contains summaries of information supporting the approval of monensin in cattle (40 FR 58289, dated December 16, 1975).

c. Residue Depletion Study

Title: "Tissue Residue Non-Interference Study in Beef Cattle Orally Treated with a Combination of Pennchlor® 100 Hi-Flo and Rumensin™ 90" (Study No. HC001-18-0720)

Study Dates: February 20, 2020, to November 17, 2020

Study Location: Tulare, California

Study Design:

Objective: The objective of this Good Laboratory Practice (GLP) study was to measure the concentrations of chlortetracycline and monensin residues in kidney and liver tissues from beef cattle treated with a combination of Pennchlor® 100 Hi-Flo (chlortetracycline Type A medicated article) and Rumensin™ 90 (monensin Type A medicated article) in Type C medicated feeds.

Study Animals: Eight crossbred beef cattle (four males and four females) were used for the study.

Experimental Design and Drug Administration: Cattle were randomly assigned to the control or treatment groups. The two control cattle were provided an unmedicated feed throughout the study. The six cattle (three males and three females) were provided approximately 500 mg/head/day monensin for the entire 10-day treatment period and approximately 10 mg/lb body weight/day chlortetracycline for the last five days of the treatment period.

Measurements: Cattle were withdrawn from their respective feeds approximately 10 hours prior to slaughter. Kidney and liver samples were collected. Kidney samples were assayed for chlortetracycline residues by a microbiological method. Liver samples were assayed for monensin residues by a thin-layer chromatography (TLC) bioautography method.

Results: None of the liver samples contained quantifiable monensin residues. The concentrations of chlortetracycline residues in all kidney samples were well below the tolerance of 12 ppm. The mean (± standard deviation) concentration of chlortetracycline in kidney samples was 1.213 (± 0.33) µg/g.

Conclusions: The data from Study HC001-18-0720 showed that residues of chlortetracycline and monensin in cattle tissues were below their respective tolerances after a 0-day withdrawal period when chlortetracycline and monensin were fed in combination. Additional data provided also showed noninterference of chlortetracycline in the analytical method for monensin and noninterference of monensin in the analytical method for chlortetracycline in cattle tissues.

2. Target Tissue(s) and Marker Residue(s)

   No reassessments for target tissues and marker residues were needed for this approval. Neither a target tissue nor a marker residue is codified for chlortetracycline in cattle (21 CFR 556.150). Neither a target tissue nor a marker residue is codified for monensin in cattle (21 CFR 556.420).

3. Tolerance(s)

   Tolerances for the sum of tetracycline residues in edible tissues of cattle are 2 ppm in muscle, 6 ppm in liver, and 12 ppm in kidney and fat (21 CFR 556.150).

   Tolerances for monensin in edible tissues of cattle are 0.10 ppm in liver and 0.05 ppm in muscle, kidney and fat (21 CFR 556.420).

4. Withdrawal Period

   The data from Study HC001-18-0720 support assignment of a 0-day withdrawal period for cattle treated with the combination of chlortetracycline and monensin in Type C medicated feed.

D. Analytical Methods for Residues

1. Determinative Method

   The microbiological method for determining chlortetracycline in cattle kidney is described in NADA 138-935 (FOI Summary, dated March 24, 1999). The TLC/bioautography method for determining monensin in cattle liver is described in NADA 095-735 (40 FR 58289, dated December 16, 1975).

2. Confirmatory Method

   Confirmatory methods were not required for chlortetracycline and monensin.

3. Availability of Method

   The validated analytical methods for analysis of residues of chlortetracycline and monensin are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, 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:

Keep this and all drugs out of the reach of children. Not for human use.

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 Pennchlor® and Rumensin™ demonstrate that, when they are used according to the label, they are safe and effective for the following indications.

1. For treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in beef calves 2 months of age and older.

2. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter over 700 lbs.

3. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter over 700 lbs.

4. For treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter.

5. For treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter.

6. For the reduction of the incidence of liver abscesses and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter over 400 lbs.

7. For the reduction of the incidence of liver abscesses and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter over 400 lbs.

8. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for the prevention and control of coccidiosis

due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter under 700 lbs.

9. For control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter under 700 lbs.

10. For the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing beef steers and heifers fed in confinement for slaughter.

11. For the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline and for improved feed efficiency in growing beef steers and heifers fed in confinement for slaughter.

Additionally, data demonstrate that residues in food products derived from beef calves 2 months of age and older, and growing beef steers and heifers fed in confinement for slaughter administered Pennchlor® and Rumensin™ 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. The veterinary feed directives issued for this drug are not refillable.

The decision to restrict this drug to use by or upon the lawful veterinary feed directive issued by a licensed veterinarian was based on the following factors: adequate directions cannot be written to enable laypersons 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 mitigate the potential for 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.