

Date of Approval: August 11, 2022

FREEDOM OF INFORMATION SUMMARY
ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-565

Pennitracin MD[®] and Coban[™]

**(bacitracin Type A medicated article) and (monensin Type A
medicated article)**

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

**Broiler chickens, laying hen replacement chickens,
and layer breeder replacement chickens**

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 141-565

B. Sponsor

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

Drug Labeler Code: 069254

C. Proprietary Names

Pennitracin MD[®] and Coban[™]

D. Drug Product Established Names

bacitracin Type A medicated article and monensin Type A medicated article

E. Pharmacological Categories

Pennitracin MD[®]: antimicrobial
Coban[™]: anticoccidial

F. Dosage Form

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

G. Amount of Active Ingredients in Currently Marketed Products¹

Pennitracin MD[®]: 50 g/lb of bacitracin (as feed grade bacitracin methylenedisalicylate)
Coban[™]: 90.7 g/lb of monensin, USP

H. How Supplied

Pennitracin MD[®]: 50 lb bag
Coban[™]: 55.12 lb bag

I. Dispensing Status

Over-the-counter (OTC)

J. Route of Administration

Oral

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 C medicated feeds that are the subject of this approval.

K. Species/Classes

Broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens

L. Indications and Dosage Regimens

1. For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in broiler chickens.

- a. 50 g/ton of bacitracin (as feed grade bacitracin methylenedisalicylate provided by Pennitracin MD[®]) for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*

- b. 90 to 110 g/ton of monensin (as Coban[™]) as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*

Feed as the sole ration for 28 to 35 days, starting from the time chicks are placed for brooding.

2. For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in laying hen replacement chickens and layer breeder replacement chickens.

- a. 50 g/ton of bacitracin (as feed grade bacitracin methylenedisalicylate provided by Pennitracin MD[®]) for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*

- b. 90 to 110 g/ton of monensin (as Coban[™]) as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*

Feed as the sole ration for 28 to 35 days, starting from the time chicks are placed for brooding.

3. For increased rate of weight gain and improved feed efficiency, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in broiler chickens.

- a. 4 to 50 g/ton of bacitracin (as feed grade bacitracin methylenedisalicylate provided by Pennitracin MD[®]) for increased rate of weight gain and improved feed efficiency

- b. 90 to 110 g/ton of monensin (as Coban[™]) as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*

Feed as the sole ration throughout the feeding period.

4. For increased rate of weight gain and improved feed efficiency, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in laying hen replacement chickens and layer breeder replacement chickens.
 - a. 4 to 50 g/ton of bacitracin (as feed grade bacitracin methylenedisalicylate provided by Pennitracin MD[®]) for increased rate of weight gain and improved feed efficiency
 - b. 90 to 110 g/ton of monensin (as Coban[™]) as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*

Feed as the sole ration throughout the feeding period.

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 bacitracin 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 Pennitracin MD[®] and Coban[™] for use in broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens, 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
Pennitracin MD® Sponsored by Pharmgate Inc.	1. For use in feeds for broiler and replacement chickens for increased rate of weight gain and improved feed efficiency. ^a 2. For use in feeds for broiler and replacement chickens for the prevention of mortality caused by necrotic enteritis associated with <i>Clostridium perfringens</i> . ^b	NADA 141-137 ^a (21 CFR 558.76(d)(1)(i)) ^b (refer to the FOI Summary, dated April 28, 2022)
Coban™* Sponsored by Elanco US Inc.	For use in feeds for broiler ^c and layer replacement ^{d**} chickens as an aid in the prevention of coccidiosis caused by <i>Eimeria necatrix</i> , <i>E. tenella</i> , <i>E. acervulina</i> , <i>E. brunetti</i> , <i>E. mivati</i> , and <i>E. maxima</i> .	NADA 038-878 ^c (as published in the FEDERAL REGISTER (35 FR 7734) on May 20, 1970, and in the FEDERAL REGISTER (39 FR 23055) on June 26, 1974) ^d (as published in the FEDERAL REGISTER (41 FR 9875) on March 8, 1976)

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

** The target animal approved in the 1976 approval for Coban™ is “replacement layer chickens intended for use as cage layers”; this target animal was revised to “laying hen replacement chickens, and layer breeder replacement chickens” 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

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 bacitracin methylenedisalicylate and monensin on the human food safety of the previously separately approved conditions of use for Pennitracin MD[®] and Coban[™] for use in broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens, 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 (antimicrobial resistance)

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 (antimicrobial resistance) 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
Pennitracin MD [®]	NADA 141-137 (as published in the FEDERAL REGISTER (80 FR 79474) on December 22, 2015)
Coban [™]	NADA 038-878 (as published in the FEDERAL REGISTER (35 FR 7734) on May 20, 1970)

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 in broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens. NADA 141-137 contains summaries of studies supporting the approval of bacitracin (as bacitracin methylenedisalicylate) in broiler and layer replacement chickens (80 FR 79474, dated December 22, 2015). NADA 038-878 contains summaries of studies supporting the approval of monensin in broiler chickens (35 FR 7734, dated May 20, 1970, and 39 FR 23055, dated June 26, 1974) and layer replacement chickens (41 FR 9875, dated March 8, 1976). The sponsor obtained a right of reference to the data and information in the NADA 038-878 file to support this approval.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval in broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens. NADA 141-137 contains summaries of studies supporting the approval of bacitracin (as bacitracin methylenedisalicylate) in broiler and layer replacement chickens (80 FR 79474, dated December 22, 2015). NADA 038-878 contains summaries of studies supporting the approval of monensin in broiler chickens (35 FR 7734, dated May 20, 1970, and 39 FR 23055, dated June 26, 1974) and layer replacement chickens (41 FR 9875, dated March 8, 1976). The sponsor obtained a right of reference to the data and information in the NADA 038-878 file to support this approval.

c. Tissue Residue Depletion Study

Because a tolerance for residues of monensin in chickens is not required (21 CFR §556.420), data and/or information on monensin residue depletion and interference with the monensin assay are not needed to support this approval. A tolerance of 0.5 ppm for bacitracin residues in chickens is codified under 21 CFR §556.70. Therefore, to satisfy the residue chemistry requirements for this ADAA feed-use combination, the sponsor needed to demonstrate tissue residue depletion non-interference and confirm that the proposed feed-use combination qualifies for a zero-day withdrawal period assignment based on the concentrations of bacitracin residues in the edible tissues and the codified bacitracin tolerance. In addition, the sponsor needed to demonstrate that monensin residues do not interfere with the assay of bacitracin residues in the edible tissues of chickens.

In *lieu* of conducting tissue residue depletion studies, the sponsor obtained a right of reference to the data and information in the NADA 049-463 file (45 FR 7787, dated February 5, 1980), and referred to the tissue residue depletion portion of "Study CK-710" in the NADA 049-463 file to support this approval. The "Study CK-710", titled

"Combination of Monensin, Roxarsone² and Bacitracin Methylene Disalicylate," was a large multipurpose study where broiler chickens received medications including monensin, roxarsone, and bacitracin methylene disalicylate in the feeds to allow for the evaluation of the 2- and 3-way combinations and to provide tissues for residue analyses from birds that received each of the individual drugs and the drug combinations at the inclusion rates shown in the study summary below. The study provided the pivotal bacitracin and monensin tissue residue data in support of the approved feed use combination of Coban™ plus BMD® under NADA 049-463.

In the human food safety evaluation for this approval of the ADAA feed-use combination of Pennitracin MD® and Coban™ (4 to 50 g/ton bacitracin methylenedisalicylate and 90 to 110 g/ton monensin) in the manufacture of Type C medicated feed for broiler chickens, CVM relied primarily on the bacitracin tissue residue data from "Study CK-710" and the supporting information from literature to show that tissue residue depletion noninterference and assay noninterference were demonstrated for this approval, and to reach the conclusion that this approval qualifies for a zero-day withdrawal period assignment. A summary of the bacitracin and monensin tissue residue depletion portion of "Study CK-710" is provided below. CVM considered Pennitracin MD® and BMD® as equal with regard to using the residue data from "Study CK-710" to support this approval.

Study Title: Combination of Monensin, Roxarsone² and Bacitracin Methylene Disalicylate

Study Design: Day-old broiler chicks were divided into treatment groups by sex and received medications including monensin, roxarsone, and bacitracin methylene disalicylate in the feeds as the individual drugs and the drug combinations for 56 days. All birds were fed non-medicated feed during the withdrawal periods.

For assay of bacitracin residues, muscle, liver, skin and fat tissue samples were collected at 0 and 24 hours of medicated feed withdrawal from 6 birds in each of the following treatment groups:

- Bacitracin Methylene Disalicylate 50 g/ton
- Bacitracin Methylene Disalicylate 50 g/ton + Monensin 110 g/ton
- Bacitracin Methylene Disalicylate 50 g/ton + Roxarsone 45.4 g/ton
- Bacitracin Methylene Disalicylate 50 g/ton + Roxarsone 45.4 g/ton + Monensin 110 g/ton

The tissue samples were assayed for bacitracin residues using a microbiological assay with a limit of quantitation of 0.1 ppm.

² The approval of this combination did not rely on the treatment groups from "Study CK 710" that contained roxarsone. The approvals of the roxarsone Type A medicated articles have been previously withdrawn (78 FR 70062, dated November 22, 2013, and 79 FR 10976, dated February 27, 2014).

For assay of monensin residues, muscle, liver, skin and fat tissue samples were collected at 0, 24 and 48 hours of medicated feed withdrawal from 6 birds in each of the following treatment groups:

- Monensin 110 g/ton
- Monensin 110 g/ton + Roxarsone 45.4 g/ton
- Monensin 110 g/ton + Bacitracin Methylene Disalicylate 50 g/ton
- Monensin 110 g/ton + Roxarsone 45.4 g/ton + Bacitracin Methylene Disalicylate 50 g/ton

Monensin residues in the tissue samples were assayed using a microbiological method with a limit of quantitation of 0.05 ppm.

Results: Bacitracin residue concentrations in all the assayed edible tissue samples at 0 and 24 hours of medicated feed withdrawal were below the method's limit of quantitation of 0.1 ppm and also below the codified bacitracin tolerance of 0.5 ppm (21 CFR §556.70), supporting a zero-day withdrawal period assignment for this approval. Data on monensin residues were not needed to support the withdrawal period assignment because a tolerance for residues of monensin in chickens is not required (21 CFR §556.420). The monensin residue data from this study, in conjunction with information from literature, supported that there was no interference by monensin with the assay of bacitracin in the study.

Conclusions: The bacitracin residue data from "Study CK-710" demonstrated tissue residue depletion noninterference and confirmed a zero-day withdrawal period assignment for this approval of the feed-use combination of Pennitracin MD[®] and Coban[™], based on the codified tolerance of 0.5 ppm for bacitracin residues in chickens (21 CFR §556.70).

Method noninterference by monensin with the assay of bacitracin in "Study CK-710" was demonstrated.

2. Target Tissues and Marker Residues

a. Bacitracin

A target tissue and marker residue have not been established for residues of bacitracin in chickens (21 CFR §556.70).

b. Monensin

A target tissue and marker residue have not been established for residues of monensin in chickens (21 CFR §556.420).

3. Tolerances

a. Bacitracin

The codified tolerance for bacitracin residues in the edible tissues of chickens is 0.5 ppm (21 CFR §556.70).

b. Monensin

A tolerance for monensin residues in the edible tissues (excluding eggs) of chickens is not required (21 CFR §556.420).

4. Withdrawal Period

The results of the tissue residue depletion portion of the study (Study CK-710) confirmed a zero-day withdrawal period assignment for this approval of the feed-use combination of Pennitracin MD[®] and Coban[™] in the manufacture of Type C medicated feed for broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens.

D. Analytical Method for Residues

An FOI Summary was not prepared for the original and supplemental approvals of NADA 049-463. The Federal Register Notice for NADA 049-463 (45 FR 7787, dated February 5, 1980) does not include a description of the validated microbiological analytical method for measuring bacitracin residues in edible chicken tissues. The validated microbiological analytical method is described in NADA 049-463.

The validated microbiological analytical method for analysis of residues of bacitracin in chicken tissues is 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.

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 Pennitracin MD[®] and Coban[™] demonstrate that, when they are used according to the label, they are safe and effective for the following indications.

1. For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in broiler chickens.
2. For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in laying hen replacement chickens and layer breeder replacement chickens.
3. For increased rate of weight gain and improved feed efficiency, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in broiler chickens.
4. For increased rate of weight gain and improved feed efficiency, and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* in laying hen replacement chickens and layer breeder replacement chickens.

Additionally, data demonstrate that residues in food products derived from broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens administered Pennitracin MD[®] and Coban[™] will not represent a public health concern when the combination medicated feed is used according to the label.

A. Marketing Status

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the labeling are reasonably certain to be followed in practice.

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.