Date of Approval: September 9, 2020

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-529

Pennitracin MD® and Maxiban™

(bacitracin Type A medicated article) and (narasin and nicarbazin Type A medicated article)

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

broiler 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 141-529

B. Sponsor

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

Drug Labeler Code: 069254

C. Proprietary Names

Pennitracin MD® and Maxiban™

D. Drug Product Established Names

bacitracin Type A medicated article and narasin and nicarbazin Type A medicated article

E. Pharmacological Categories

Pennitracin MD®: antimicrobial
Maxiban™: 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 Products[1]

Pennitracin MD®: 50 g/lb bacitracin (as feed grade bacitracin methylenedisalicylate)
Maxiban™: 36 g/lb narasin and 36 g/lb nicarbazin (1:1 ratio)[2]

H. How Supplied

Pennitracin MD®: 50 lb bag
Maxiban™: 55.12 lb bag

I. Dispensing Status

Over-the-counter (OTC)

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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 C medicated feeds that are the subject of this approval.
[2] Narasin and nicarbazin may only be sourced from Maxiban™, NADA 138-952, which provides these two drugs at a 1:1 ratio.

J. Route of Administration

Oral

K. Species/Class

Broiler chickens

L. Indications and Dosage Regimen

1. For increased rate of weight gain and improved feed efficiency, and for 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. 27 to 45 g/ton each of narasin and nicarbazin (as Maxiban™) for the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*

    Feed continuously as the sole ration.

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 narasin and nicarbazin Type A medicated article on the effectiveness and target animal safety of the previously separately approved conditions of use for Pennitracin MD® and Maxiban™ for use in broiler 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.	For use in feeds for broiler chickens for increased rate of weight gain and improved feed efficiency.	NADA 141-137 (refer to 21 CFR 558.76(e)(1)(ii))
Maxiban™* Sponsored by Elanco US Inc.	For use in feeds for broiler chickens for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*.	NADA 138-952 (refer to the FOI Summary, dated January 18, 1989)

*Elanco US Inc. has provided Pharmgate, Inc. right of reference to use Maxiban™ 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 bacitracin (as bacitracin methylenedisalicylate), narasin, and nicarbazin on the human food safety of the previously separately approved conditions of use for Pennitracin MD® and Maxiban™ for use in broiler 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

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
Pennitracin MD®	NADA 141-137 (as published in the FEDERAL REGISTER (80 FR 79474) on December 22, 2015)
Maxiban™	NADA 138-952 (refer to the FOI Summary, dated July 11, 2018)

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

   CVM did not require total residue and metabolism studies for this approval. NADA 141-137 contains summaries of studies supporting the approval of bacitracin (as bacitracin methylenedisalicylate) in broiler chickens (80 FR 79474, dated December 22, 2015). The FOI Summary for the original approval of NADA 118-980 dated August 14, 1986, contains a summary of total residue and metabolism studies for narasin in broiler chickens. The FOI Summary for the supplemental approval of NADA 138-952 dated July 11, 2018, contains a summary of total residue and metabolism studies for nicarbazin in broiler chickens.

   b. Comparative Metabolism Study

   CVM did not require comparative metabolism studies for this approval. NADA 141-137 contains summaries of studies supporting the approval of bacitracin (as bacitracin methylenedisalicylate) in broiler chickens

(80 FR 79474, dated December 22, 2015). The FOI Summary for the original approval of NADA 118-980 dated August 14, 1986, contains a summary of comparative metabolism studies for narasin in broiler chickens. The FOI Summary for the supplemental approval of NADA 138-952 dated July 11, 2018, contains a summary of comparative metabolism studies for nicarbazin in broiler chickens.

c. Tissue Residue Depletion Study

In lieu of conducting tissue residue depletion studies, the sponsor obtained a right of reference to data and information in the NADA 140-926 file (approved combination use of BMD® and Maxiban™ for use in the manufacture of Type C medicated feed for broiler chickens) for supporting this approval. CVM relied on the tissue residue depletion study No. AAC8721 in NADA 140-926 file to demonstrate tissue residue depletion noninterference and assay noninterference for this approval, and to reach the conclusion that the combination of Pennitracin MD® and Maxiban™ for use in the manufacture of Type C medicated feed for broiler chickens (4 to 50 g bacitracin (as bacitracin methylenedisalicylate)/ton, 27 to 45 g narasin/ton and 27 to 45 g nicarbazin/ton of feed) qualifies for a zero-day withdrawal period assignment. The study No. AAC8721 has been described in the FOI Summary for the original approval of NADA 140-926 dated January 04, 1999. A brief summary of the study is provided below to show how the residue data from that study were used to support this approval.

Title: Tissue residue non-interference study in broiler poultry medicated with narasin (50 ppm), nicarbazin (50 ppm), and bacitracin methylenedisalicylate (200 g/ton) - Study No. AAC8721

Study Dates: October 15, 1987, to August 3, 1988

Study Location: Indiana, United States

Study Design: In the study, day-old chicks were fed broiler ration medicated with 50 ppm (45.4 g/ton) narasin, 50 ppm (45.4 g/ton) nicarbazin, and 200 g/ton bacitracin methylenedisalicylate for 49 days. Four males and four females were slaughtered at 6 hours (practical zero withdrawal for chickens) and at 1, 2, or 4 days following withdrawal of the medicated feed. Bacitracin residue concentration in muscle, narasin residue concentration in abdominal fat, and nicarbazin residue concentration in liver were determined.

Results: The residue data at zero withdrawal from the study are shown below:

Table III.2. Mean (ppm) and Standard Deviation (SD) of Bacitracin, Narasin and Nicarbazin Residue Concentrations in Tissues of Broiler Chickens at Zero Withdrawal after Treatment

Drug Residue	Tissue	Animal Number	Mean (ppm) ± SD
Bacitracin	Muscle	4 M+ 4 F	<0.3
Narasin	Abdominal Fat	3 M+ 3 F	0.030 ± 0.009
Nicarbazin	Liver	4 M+ 4 F	8.50 ± 2.96

The 99th percentile upper tolerance limit with 95% confidence was not calculated for bacitracin residues in muscle at zero withdrawal, because the bacitracin residue concentrations in muscle were all below the detection limit for bacitracin (0.3 ppm), which was below the codified tolerance of 0.5 ppm for bacitracin in muscle (21 CFR 556.70).

At zero withdrawal, the 99th percentile upper tolerance limit with 95% confidence for narasin in abdominal fat was 75.6 ppb, below the codified tolerance of 480 ppb for narasin (marker residue) in chicken abdominal fat (target tissue, 21 CFR 556.428).

At zero withdrawal, the 99th percentile upper tolerance limit with 95% confidence for nicarbazin (4,4′-dinitrocarbanilide) in liver was 21.39 ppm, below the codified tolerance of 52 ppm for 4,4′-dinitrocarbanilide (marker residue for nicarbazin) in chicken liver (target tissue, 21 CFR 556.445).

Study No. AAC8721 also demonstrated noninterference of the analytical methods for narasin, nicarbazin and bacitracin. Therefore, CVM did not require additional studies to demonstrate assay noninterference for this approval.

Conclusion: The results of study No. AAC8721 demonstrated tissue residue depletion noninterference and assay noninterference and confirmed a zero-day withdrawal period assignment for the combination of Pennitracin MD® and Maxiban™ 72 for use in Type C medicated feed for broiler chickens (4 to 50 g bacitracin (as bacitracin methylenedisalicylate)/ton, 27 to 45 g narasin/ton and 27 to 45 g nicarbazin/ton of feed).

2. Target Tissues and Marker Residues

   a. Bacitracin

      A target tissue and a marker residue have not been established for bacitracin in chickens (NADA 141-137, 80 FR 79474, dated December 22, 2015).

   b. Narasin

      The target tissue for narasin is abdominal fat. The marker residue is parent narasin (NADA 118-980, FOI Summary dated April 11, 2001).

c. Nicarbazin

The target tissue for nicarbazin is liver. The marker residue for nicarbazin is 4,4′-dinitrocarbanilide (NADA 138-952, FOI Summary dated July 11, 2018).

3. Tolerances

a. Bacitracin

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

b. Narasin

The codified tolerance for parent narasin in chicken abdominal fat is 480 ppb (NADA 118-980, FOI Summary dated April 11, 2001; 21 CFR 556.428).

c. Nicarbazin

The codified tolerance for 4,4′-dinitrocarbanilide in chicken liver is 52 ppm (NADA 138-952, FOI Summary dated July 11, 2018, 21 CFR 556.445).

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

The results of study No. AAC8721 confirmed a zero-day withdrawal period assignment for the combination of Pennitracin MD® and Maxiban™ for use in Type C medicated feed for broiler chickens (4 to 50 g bacitracin (as bacitracin methylenedisalicylate)/ton, 27 to 45 g narasin/ton and 27 to 45 g nicarbazin/ton).

D. Analytical Method for Residues

Analytical methods for the individual drugs in this combination are described in NADA 140-926 for combination use of BMD® and Maxiban™ in chicken feed (FOI Summary dated January 04, 1999).

The validated analytical methods for analysis of residues of bacitracin, narasin and nicarbazin in chicken tissues 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.

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 Maxiban™ demonstrate that, when they are used

according to the label, they are safe and effective for increased rate of weight gain and improved feed efficiency, and for the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina, E. brunetti*, *E. mivati*, and *E. maxima* in broiler chickens. Additionally, data demonstrate that residues in food products derived from chickens administered Pennitracin MD® and Maxiban™ 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 OTC because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label 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.