Date of Approval: September 6, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-429

Stafac® and Maxiban™

(virginiamycin) 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 indication listed in Section I.L.

Sponsored by:

Phibro Animal Health Corp.

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I. GENERAL INFORMATION

A. File Number

NADA 141-429

B. Sponsor

Phibro Animal Health Corp.
GlenPointe Centre East, 3rd floor
300 Frank W. Burr Blvd., suite 21
Teaneck, NJ 07666

Drug Labeler Code: 066104

C. Proprietary Names

Stafac® and Maxiban™

D. Drug Product Established Names

virginiamycin and narasin and nicarbazin Type A medicated article

E. Pharmacological Categories

Stafac®: 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]

Stafac®: 20, 50, or 227 g/lb of virginiamycin
Maxiban™: 36 g/lb narasin and 36 g/lb nicarbazin

H. How Supplied

Stafac®: 50 lb or 55 lb bags, 1323 lb or 1764 lb totes
Maxiban™: 55.12 lb bag

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 C medicated feeds that are the subject of this approval.

J. Route of Administration

Oral

K. Species/Class

Broiler chickens

L. Indication and Dosage Regimen

1. For prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin 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. 20 g/ton of virginiamycin (as Stafac®) for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin.

    b. 54 to 90 g/ton of narasin and nicarbazin (as Maxiban™; 27 to 45 g/ton narasin and 27 to 45 g/ton nicarbazin, in a 1:1 ratio to create 54 to 90 g/ton) for the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*.

    Feed as the sole ration.

II. EFFECTIVENESS

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 when certain conditions are met. In those cases, the FD&C Act provides that effectiveness of each drug, demonstrated in its NADA at the time of the approval, are adequate. The Agency has based its determination of the effectiveness of the combination of virginiamycin and narasin and nicarbazin Type A medicated article on the effectiveness of the previously separately approved conditions of use for Stafac® 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;

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 for the individual drugs subject to this combination.

Drug Product	Indication	Approval Information
Stafac® Sponsored by Phibro Animal Health Corp.	For use in feeds for broiler chickens for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin.	NADA 091-467 (as published in the FEDERAL REGISTER (46 FR 18966) on March 27, 1981)
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 Phibro Animal Health Corp. right of reference to use Maxiban™ in this combination.

III. TARGET ANIMAL SAFETY

The FD&C Act, as amended by the ADAA of 1996, allows for drugs to be fed in combination in Type C medicated feeds without additional demonstration of their target animal safety when each drug or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- 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.

CVM determined that there was a substantiated scientific concern based on study data previously submitted to CVM for the combination use of virginiamycin and narasin in the Type C medicated feed in broiler chickens. These data indicated an increase in *Eimeria tenella* lesion scores and mortality associated with virginiamycin, either alone or fed in combination with narasin, in the presence of a coccidial infection. In addition, previously submitted data also indicated an increase in mortality specifically when virginiamycin was fed in combination with narasin and nicarbazin. The target animal safety concerns regarding increase in *E. tenella* lesion scores and mortality were addressed in two parts (described below): A) a written justification describing the impact that lesions associated with *E. tenella* have on the growth performance of broiler chickens, and B) a study confirming that feeding Type C medicated feed containing virginiamycin, narasin, and nicarbazin in combination to broiler chickens under current management practices does not impact mortality.

A. Impact of *E. tenella* lesions on the performance of broiler chickens

Johnson and Reid (1970)[2] lesion scoring system is a tool for evaluating the severity of coccidiosis in chickens. In this system, a lesion score of 0 to 4 is assigned to a bird, where 0 = normal and 4 = most severe. As coccidiosis caused by *E. tenella* becomes more severe, bird performance, measured by changes in body weight gain and feed efficiency, may be negatively affected.

The data from the study titled "Anticoccidial Efficacy of Narasin in the Presence and Absence of Virginiamycin" (Bafundo et al., 1988)[3] was used in the written justification to address the concern regarding increased *E. tenella* lesion scores associated with feeding Type C medicated feed containing virginiamycin in chickens. The study included ten individual trials using different *Eimeria* species. Data from the *E. tenella* trialsindicated an increase in *E. tenella* lesion scores for broiler chickens that were fed Type C medicated feed containing virginiamycin alone, or in combination with narasin, during a coccidiosis infection. The birds were placed in battery pens and inoculated with *E. tenella* in an effort to elicit clinical coccidiosis. This type of study is generally designed to ensure that each bird receives a dose sufficient to produce overt signs of coccidial infection with concomitant performance losses. Tables III.1 and III.2 provide the performance and lesion score results from the two trials completed in broiler chickens that were infected with *E. tenella* (approximately 35,000 oocysts per bird).

Table III.1. Performance and lesion score results for broiler chickens infected with *E. tenella*, Trial No. T2N8C8595.

Treatment Group	Body Weight Gain (g)	Feed:Gain (g/g)	Lesion score
Unmedicated control	268.8	1.638	2.69
20 g/ton virginiamycin	252.6	1.679	3.38
54 g/ton narasin	285.6	1.586	0.88
20 g/ton virginiamycin + 54 g/ton narasin	279.6	1.622	1.38

Table III.2. Performance and lesion score results for broiler chickens infected with *E. tenella*, Trial No. T2N8C85B4.

Treatment Group	Body Weight Gain (g)	Feed:Gain (g/g)	Lesion score
Unmedicated control	257.1	1.681	3.29
20 g/ton virginiamycin	228.8	1.763	3.50
54 g/ton narasin	288.8	1.561	0.63
20 g/ton virginiamycin	289.2	1.560	2.56

[2] Johnson, J. and W. M. Reid. 1970. Anticoccidial drugs: Lesion scoring techniques in battery and floor-pen experiments with chickens. Exp. Parasitol. 28:30-36.
[3] Bafundo, K. W., D. J. Donovan, and L. V. Tonkinson. 1988. Unpublished data.

Treatment Group	Body Weight Gain (g)	Feed:Gain (g/g)	Lesion score
+ 54 g/ton narasin			

As shown, bird performance was not affected when virginiamycin and narasin were fed in combination, despite the increase in lesion scores compared to narasin fed alone. These observations are consistent with a report by Conway et al. (1990)[4] who observed only subtle changes in body weight with increasing severity of *E. tenella* lesions and noted meaningful changes in body weight only when lesion scores approached 4 on the Johnson and Reid lesion scoring system.

Conclusion: The use of virginiamycin and narasin fed in combination in Type C medicated feed is not expected to impact the safety of broiler chickens, as any deleterious effects of an increase in lesion scores on bird health would directly impact growth performance factors.

B. Margin of Safety Study: Mortality

Title: Non-Clinical Laboratory Study (GLP): Supplemental evaluation of the safety of an antibiotic (virginiamycin; Stafac®) in combination with an anticoccidial product containing either narasin alone (Monteban™)[5] or in combination product containing narasin and nicarbazin (Maxiban™) in broiler chickens housed in floor pens; Study No. HMS 082114

Study Dates: February 15, 2015 to April 28, 2015

Study Location: Tulare, California

Study Design:

Objective: To evaluate if feeding the combination of Stafac® and Maxiban™ to broiler chickens increased mortality under current commercial management and rearing practices.

Pre-study Seeding of the Litter: On Study Day -28, 180 10- to 14- day-old broiler chicks were inoculated via oral gavage into the crop with a 1- mL dose of sporulated oocysts containing *E. tenella* (5×10^3 oocysts per dose) and *E. maxima* (1×10^4 oocysts per dose). Of the seven species of coccidia that Maxiban™ is indicated to have a therapeutic effect against, *E. tenella* and *E. maxima* were selected because both species are commonly present in commercial

[4] Conway, D. P., M. E. McKenzie, and A. D. Dayton. 1990. Relationship of coccidial lesion scores and weight gain in infections of *Eimeria acervulina*, *E. maxima*, and *E. tenella* in broilers. Avian Pathol. 19: 489-496.

[5] The combination of Stafac® and Monteban™ was included as a third treatment group in this study in support of an approval under NADA 141-462. Information pertaining to results from that treatment group were not considered in support of the Stafac® and Maxiban™ approval, and therefore are not presented in this FOI Summary. Data pertaining to the Stafac® and Monteban™ treatment group may be found in the FOI Summary for NADA 141-462.

broiler houses and were expected to cause at least a subclinical infection in some birds at the level dosed. Five inoculated birds were placed on used litter (wood shavings) in each of 36 pens. All birds were provided *ad libitum* access to unmedicated feed and water. These birds remained in the pens for 24 days to naturally infect (seed) the litter with coccidia oocysts shed in the feces. They were removed from pens on Study Day -2.

Study Animals: A total of 1,800 healthy day-old Cobb x Cobb-strain broiler chickens (900 males, 900 females) were enrolled in the study. Each was assigned a uniquely numbered wing band for identification.

Experimental Design: Twenty-five male and twenty-five female chicks were assigned to each of the eighteen pens assigned to each treatment group.

Drug Administration*:* The control diet, a non-medicated feed, was provided to treatment group TG01. The test diet, a Type C medicated feed, was provided to treatment group TG02. This Type C medicated test feed was mixed to contain 20 g/ton virginiamycin (NADA 091-467) and 90 g/ton narasin and nicarbazin (45 g narasin/ton and 45 g nicarbazin/ton) (NADA 138-952). Dietary treatments were administered in commercial poultry feeds appropriate for the birds' age and stage of production. Feed and clean, unmedicated water were provided *ad libitum* for the duration of the study*.*

Chicks received no vaccinations at the hatchery or upon arrival at the farm. In addition, no concomitant therapy was allowed during this study. Individual animals requiring therapy were removed from the study.

Measurements and Observations: Initial health exams were performed on each chick on Day 0, prior to allocation and placement in specific treatment pens. Birds were observed twice daily for general health observations throughout the study. Any bird found dead or moribund during the study was necropsied to determine the most probable cause of death or moribundity. Environmental conditions within the house were monitored twice daily.

Birds (by pen), feed, and water were weighed for all treatment pens on Study Days 0, 21, 37, and 42. All feed and water were discarded after weighing.

Statistical Methods: This study used a randomized complete block design with a one-way treatment structure. The pen represented the experimental unit and three contiguous pens constituted a block. There were 18 blocks for a total of 54 floor pens, allowing for equal representation of treatment within each block.

The mortality data were analyzed using a generalized mixed linear model where the mortality per pen was assumed to be distributed as binomial. Treatment was a fixed effect and replication (block) and treatment x block interactions were random effects. Safety was tested using a one-sided alpha of 0.05. The alternative hypothesis was if mortality rate of the test product was larger than the mortality rate of the control.

Mean final live weight per bird and feed conversion for each treatment group was calculated, but not analyzed statistically.

Results:

General Health Observations: The most common health observations were lameness and depression. The total number of these observations was greatest in control birds (34 birds in TG01 vs. 15 birds in TG02). These observations are consistent with commercial poultry production and because the number of observations was lower in the treated group, the observations were determined not to be attributable to the combination use of virginiamycin, narasin, and nicarbazin.

Live Performance: The mean individual bird body weight gain (calculated from data collected per pen) and feed intake were reduced for birds in TG01 in comparison with birds in TG02, as shown in Table III.3.

Table III.3. Mean individual bird body weight gain and feed conversion ratio by pen.

Treatment Group	Body Weight Gain (g)	Feed:Gain (g/g)
Unmedicated control, TG01	2604	1.784
20 g/ton virginiamycin + 45 g/ton narasin + 45 g/ton nicarbazin, TG02	2682	1.729

Mortality and Moribundity: Variables of interest under this study were mortality and moribundity due to coccidiosis were closely monitored. Mortality rates were significantly decreased (P=0.0011) for TG02 birds (0.009%) in comparison with TG01 controls (0.03470%). The causes of death or moribundity that were unrelated to coccidiosis are consistent with common findings in commercial poultry production. Thirty-one birds in TG01 and 8 birds in TG02 were either removed (euthanized) or found dead and had a non-scheduled necropsy performed. Causes of death or moribundity for these animals are presented in Table III.4.

Table III.4. Causes of death or moribundity diagnosed during necropsy.

Diagnosis	# birds diagnosed in TG01	# birds diagnosed in TG02
Coccidiosis	9	1
Enteritis (coccidiosis present)	4	0
Bacterial infection	10	1

Diagnosis	# birds diagnosed in TG01	# birds diagnosed in TG02
Other*	8	6
Total	31	8

*Other includes: yolk sac infection, inadequate feed intake, bone/structure issues, gout, heart attack, unknown cause of death, etc.

Adverse Reactions: No treatment-related adverse reactions were reported in this study.

Conclusion: The margin of safety for the combination of virginiamycin, narasin, and nicarbazin is considered adequate because there was a reduction in mortality when compared to untreated controls.

IV. 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 virginiamycin, narasin and nicarbazin on the human food safety of the previously separately approved conditions of use for Stafac® 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.

C. 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.

D. 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 IV.1.):

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

Drug Product	Approval Information
Stafac®	NADA 091-467 (as published in the FEDERAL REGISTER (46 FR 18966) on March 27, 1981)
Maxiban™	NADA 138-952 (refer to the FOI Summary, dated January 18, 1989)

E. 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 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981). 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 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981). 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. Residue Depletion Study

Title: Tissue Residue Non-Interference Study in Broiler Poultry Medicated with ^{14}C-Virginiamycin (20 g/ton), Narasin (50 ppm), and Nicarbazin (50 ppm) (Study No. V-M-4047-87)

Study Dates: September 1987, to September 1988

Study Locations:

In Life Phase: West Chester, Pennsylvania

Analytical Phase for Determination of Tissue Residue Concentrations –

- Virginiamycin – West Chester, Pennsylvania
- Narasin – Greenfield, Indiana
- Nicarbazin – Greenfield, Indiana

Study Design: Hubbard cross broiler chicks were obtained at one day of age for use in the study. Chickens were assigned randomly to control groups or medicated groups (4 females and 4 males/group) as shown in Table IV.2. Beginning at 2 days of age, the chickens in medicated groups were given a medicated feed containing virginiamycin (20 g/ton), narasin (50 ppm) and/or nicarbazin (50 ppm) for 45 days (21 days of starter ration and 24 days of finisher ration) based on the medication schedule shown in Table IV.2. After withdrawal of the medicated feeds in finisher ration, the treated groups were fed withdrawal rations, as appropriate.

Group III chickens were slaughtered at zero withdrawal, which was 6 hours after withdrawal of the medicated feed containing ^{14}C-virginiamycin (20 g/ton), narasin (50 ppm) and nicarbazin (50 ppm) in finisher ration. Muscle, liver, and skin/fat samples were collected and analyzed for ^{14}C-virginiamycin equivalents using combustion/scintillation counting.

Chickens from Group IV were divided into 5 sub-groups, IV(A) to IV(E) (4 male and 4 female each), as shown in Table IV.2. Chickens from Group IV(A) were slaughtered at zero withdrawal, which was 6 hours after cessation of the medicated feed containing virginiamycin (20 g/ton), narasin (50 ppm), and nicarbazin (50 ppm) in finisher ration. Chickens from IV(B), IV(C), IV(D) and IV(E) were slaughtered at 1, 2, 3 and 5 days withdrawal, respectively. Abdominal fat pads (target tissue for narasin) and livers (target tissue for nicarbazin) were collected and analyzed for narasin and nicarbazin, respectively. Narasin analysis was conducted by a thin layer bioautographic method. Nicarbazin analysis was performed using a high-performance liquid chromatography (HPLC) method.

Table IV.2. Medication schedule

Group	Type and composition of ration	Feeding duration (days)
I (control)	Non-medicated starter ration	21
I (control)	Non-medicated finisher ration	24

Group	Type and composition of ration	Feeding duration (days)
II (control)	Non-medicated starter ration	21
II (control)	Non-medicated finisher ration	24
III	Starter ration (50 ppm narasin, 50 ppm nicarbazin)	21
III	Finisher ration (20 g/ton ^{14}C-virginiamycin, 50 ppm narasin, 50 ppm nicarbazin)	24
IV (A to E)*	Starter ration (20 g/ton virginiamycin, 50 ppm narasin, 50 ppm nicarbazin)	21
IV (A to E)	Finisher ration (20 g/ton virginiamycin, 50 ppm narasin, 50 ppm nicarbazin)	24
IV(B)	Withdrawal ration (20 g/ton virginiamycin)	1
IV(C)	Withdrawal ration (20 g/ton virginiamycin)	2
IV(D)	Withdrawal ration (20 g/ton virginiamycin)	3
IV(E)	Withdrawal ration (20 g/ton virginiamycin)	5

*Group IV was divided into 5 sub-groups (4 male and 4 female each) for 0 (IV(A)), 1 (IV(B)), 2 (IV(C)), 3 (IV(D)) and 5 (IV(E)) days withdrawal.

Results: At practical zero withdrawal, the mean residue concentrations of virginiamycin were < 0.019 ppm in muscle, < 0.063 ppm in skin/fat and 0.143 ppm in liver, which were well below the virginiamycin safe concentrations of 30 ppm in muscle, 60 ppm in skin/fat and 90 ppm in liver (46 FR 18966, March 27, 1981).

The mean (± standard deviation) narasin residue concentration in abdominal fat samples at practical zero withdrawal was 0.033 (± 0.015) ppm. The calculated 99th percentile upper tolerance limit with 95% confidence was 0.102 ppm, below the codified tolerance of 480 ppb for parent narasin in chicken abdominal fat.

The mean nicarbazin residue concentrations in livers of broiler chickens are presented in Table IV.3. At practical zero withdrawal, the calculated 99th percentile upper tolerance limit with 95% confidence was 25.051 ppm, below the codified tolerance of 52 ppm for 4,4'-dinitrocarbanilide (marker residue for nicarbazin) in chicken liver.

Table IV.3. Mean (± standard deviation) nicarbazin residue concentrations in livers of broiler chickens.

Withdrawal Period (Days)	Nicarbazin Concentration (ppm)
0	16.5 ± 1.97
1	10.3 ± 1.11
2	4.69 ± 0.65
3	2.75 ± 0.52
5	0.34 ± 0.17

Conclusions: The data from Study V-M-4047-87 support a zero-day withdrawal period assignment for the combination of virginiamycin (20 g/ton), narasin (27 to 45 g/ton) and nicarbazin (27 to 45 g/ton) in Type C medicated feed for use in broiler chickens. Additional information provided also showed assay noninterference for the combination use of virginiamycin, narasin and nicarbazin in edible tissues of broiler chickens.

2. Target Tissues and Marker Residues

   A target tissue and a marker residue have not been established for virginiamycin in chickens.

   The target tissue for narasin is abdominal fat, and the marker residue is parent narasin (NADA 118-980, FOI Summary dated April 11, 2001; 21 CFR §556.428).

   The target tissue for nicarbazin is liver, and the marker residue for nicarbazin is 4,4'-dinitrocarbanilide (NADA 138-952, FOI Summary dated July 11, 2018; 21 CFR §556.445).

3. Tolerances

   A tolerance for residues of virginiamycin in chickens is not required (21 CFR §556.750).

   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).

   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

   A zero-day withdrawal period is assigned for the combination of virginiamycin (20 g/ton), narasin (27 to 45 g/ton) and nicarbazin (27 to 45 g/ton) in Type C medicated feed for use in broiler chickens.

F. Analytical Method for Residues

1. Determinative Method

An analytical method is not needed for virginiamycin because total residues of virginiamycin in broiler chicken tissues at zero withdrawal do not exceed the safe concentrations for virginiamycin (46 FR 18966, dated March 27, 1981).

A thin-layer chromatography bioautographic method for determining narasin in chicken tissues is described in NADA 118-980 (FOI Summary, dated April 11, 2001).

A high-performance liquid chromatography method is used for determination of nicarbazin residues in chicken tissues.

2. Confirmatory Method

An analytical method is not needed for virginiamycin because total residues of virginiamycin in broiler chicken tissues at zero withdrawal do not exceed the safe concentrations for virginiamycin (46 FR 18966, dated March 27, 1981).

A confirmatory method for narasin was not required (FOI Summary for NADA 118-980, dated August 14, 1986).

A liquid chromatography-thermospray mass spectrometry method is used for confirmation of nicarbazin residues in chicken tissues.

3. Availability of Method

The validated analytical methods for analysis of residues of 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

V. 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 C medicated feed:

Not for human use. Keep out of reach of children.

VI. 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 Stafac® and Maxiban™ demonstrate that, when they are used according to the label, they are safe and effective for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin 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 broiler chickens administered Stafac® and Maxiban™ will not represent a public health concern when the combination medicated feed is used according to the label.

A. Marketing Status

A valid veterinary feed directive (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 VFDs 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 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 or prevent 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.