Date of Approval: September 6, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-462

Stafac® and Monteban™

(virginiamycin) and (narasin 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 141-462

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 Monteban™

D. Drug Product Established Names

virginiamycin and narasin Type A medicated article

E. Pharmacological Categories

Stafac®: antimicrobial
Monteban™: 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
Monteban™: 45 g/lb of narasin

H. How Supplied

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

I. Dispensing Status

Veterinary feed directive (VFD)

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/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 (as Monteban™) 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 or target animal safety 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 Type A medicated article on the effectiveness and target animal safety of the previously separately approved conditions of use for Stafac® and Monteban™ 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 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	Indications	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)
Monteban™* 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 118-980 (FOI Summaries, dated August 14, 1986, and March 2, 2012)

*Elanco US Inc. has provided Phibro Animal Health Corp. right of reference to use Monteban™ 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. 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 and narasin 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* trials indicated 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

[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.

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 + 54 g/ton narasin	289.2	1.560	2.56

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 the 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™) or in combination product containing narasin and nicarbazin (Maxiban®)[5] 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 Monteban™ 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

[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 Maxiban™ was included as a third treatment group in this study in support of an approval under NADA 141-429. Information pertaining to results from that treatment group was not considered in support of the Stafac® and Monteban™ approval, and, therefore, is not presented in this FOI Summary. Data pertaining to the Stafac® and Maxiban™ treatment group may be found in the FOI Summary for NADA 141-429.

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 Monteban™ is indicated to have a therapeutic effect against, *E. tenella* and *E. maxima* were selected because both species are commonly present in commercial 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 TG03. This Type C medicated test feed was mixed to contain 20 g/ton virginiamycin (NADA 091-467) and 72 g/ton narasin (NADA 118-980). 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) was a random effect. Statistical significance was evaluated at a 2-sided alpha=0.10. Safety was concluded if the null hypothesis, the mortality rate of the test product was equal to the mortality rate of the control, is rejected.

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. 23 birds in TG03). 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 and narasin.

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 TG03, 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 + 72 g/ton narasin, TG03	2706	1.728

Mortality and Moribundity: Variables of interest under this study, mortality and moribundity due to coccidiosis were closely monitored. There was no significant difference in mortality rates between TG01 (3.5%) and TG03 birds (2.2%). 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 16 birds in TG03 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 TG03
Coccidiosis	9	3
Enteritis (coccidiosis present)	4	1
Bacterial infection	10	5
Other*	8	7
Total	31	16

*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 and narasin is considered adequate because there was no increase 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 and narasin on the human food safety of the previously separately approved conditions of use for Stafac® and Monteban™ 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 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)
Monteban™	NADA 118-980 (refer to the FOI Summary, dated August 14, 1986)

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 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981). The FOI Summaries for the original approval of NADA 118-980 dated August 14, 1986, and the supplemental approval dated April 11, 2001, contain summaries of residue chemistry studies for narasin 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 Summaries for the original approval of NADA 118-980 dated August 14, 1986, and the supplemental approval dated April 11, 2001, contain summaries of residue chemistry studies for narasin in broiler chickens.

   c. Residue Depletion Study

      Title: Tissue Residue Interference Study in Broiler Poultry Medicated with ^{14}C-Virginiamycin (20 g/ton) and Roxarsone (45.4 g/ton) with Narasin (73 g/ton) (Study No. V-M-4021-83)

      Study Dates: May 25, 1983, to February 17, 1986

Study Locations:

In-Life Phase: West Chester, Pennsylvania

Analytical Phase for Determination of Tissue Residue Concentrations:
- Virginiamycin - West Chester, Pennsylvania
- Narasin - Greenfield, Indiana

Study Design:

Objective: To confirm a zero-day withdrawal period assignment for broiler chickens treated with the combination of virginiamycin at 20 g/ton and narasin at up to 72 g/ton[6] in Type C medicated feed. In the study, chickens were treated with the 3-way combination of virginiamycin, narasin and roxarsone[7] to support the 2-way combination of virginiamycin and narasin.

Study Animals: White Mountain cross broiler chicks one day of age at enrollment.

Experimental Design: The animals were randomly assigned to the treatment groups, with an equal number of males and females in each group, as shown in Table III.2 below.

Drug Administration: The medication schedule for virginiamycin (Vm, 20 g/ton), roxarsone (Rox, 45.4 g/ton) and/or narasin (Nar, 73 g/ton) is shown in Table III.2. Administration of medicated feed began at 2 days of age. The treated groups were fed medicated feeds in starter ration for 21 days, followed by medicated feeds in finisher ration for 24 days. After withdrawal of the medicated feeds in finisher ration, the treated groups were fed withdrawal rations, as appropriate, and slaughtered for tissue sample collections.

Table IV.2. Medication schedule

Group (number of chickens)	Medicated feed (starter ration) for 21 days	Medicated feed (finisher ration) for 24 days	Withdrawal ration (days)
Control (24)	NA*	NA	NA
SKF-I (10)	Rox + Nar‡	Rox + Nar	NA
SKF-II (10)	Rox + Nar	^{14}C-Vm + Rox + Nar	NA
SALS-I (34)	Vm§ + Nar	Vm + Nar	Vm + Nar (2), followed by Vm (3)

[6] To ensure chickens received 72 g/ton of narasin, medicated feed was prepared at 73 g/ton narasin

[7] The approval of this combination did not rely on the data from the roxarsone treatment group. 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).

Group (number of chickens)	Medicated feed (starter ration) for 21 days	Medicated feed (finisher ration) for 24 days	Withdrawal ration (days)
Statistical method	Vm + Rox + Nar	Vm + Rox + Nar	Vm + Nar (2), followed by Vm (3)
EL-I (34)	Vm + Rox	Vm + Rox	Vm (7)
EL-II (34)	Vm + Rox + Nar	Vm + Rox + Nar	Vm + Nar (2), followed by Vm (5)

* NA, not applicable
Rox, roxarsone
‡ Nar, narasin
§ Vm, virginiamycin

Measurements: Group SKF-II chickens were slaughtered at practical zero withdrawal, which was 6 hours after withdrawal of the medicated feed containing ^{14}C-virginiamycin (20 g/ton), roxarsone (45.4 g/ton), and narasin (73 g/ton) in finisher ration. Muscle, liver, and skin/fat samples were collected and assayed for ^{14}C-virginiamycin equivalents using combustion/scintillation counting.

Chickens from Groups SALS-I and SASL-II were slaughtered at 0 (practical zero), 1, and 3 days withdrawal from narasin. Chickens from Group EL-II were slaughtered at 0 (practical zero), 2, 3, and 5 days withdrawal from narasin. Skin/fat samples were collected and assayed for parent narasin concentrations using a thin-layer bioautographic method.

The information about tissue sample collection and assay for roxarsone residues (as arsenic) are not included in this FOI Summary because the results were not used for supporting this approval.

Results: At practical zero withdrawal, the highest residue concentrations of virginiamycin were < 0.06 ppm in muscle, < 0.10 ppm in skin/fat and 0.22 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).

As shown in Table III.3 below, at practical zero withdrawal, the highest parent narasin residue concentration in skin/fat samples from the chickens fed the medicated feed containing virginiamycin (20 g/ton), roxarsone (45.4 g/ton), and narasin (73 g/ton) was 34 ppb. The calculated 99th percentile upper tolerance limit with 95% confidence was 54 ppb, well below the codified tolerance of 480 ppb for parent narasin in chicken abdominal fat. At 2, 3 and 5 days withdrawal, the parent narasin residue concentrations in skin/fat samples were even lower than those at practical zero withdrawal.

Table IV.3. Highest narasin residue concentrations in skin/fat samples from chickens fed medicated feed containing virginiamycin (20 g/ton), roxarsone (45.4 g/ton) and narasin (73 g/ton)

Chickens males/females	Withdrawal of narasin from withdrawal ration (days)	Parent narasin concentration (ppb)
4/4	0	34
4/4	2	< 5
3/4	3	6
4/4	5	< 5

The study results support a zero-day withdrawal period assignment for the combination of virginiamycin (20 g/ton) and narasin (up to 73 g/ton). Additional information provided in the study also showed that the presence of virginiamycin in skin/fat tissues does not interfere with the assay for narasin. However, the study alone is not sufficient to support a zero-day withdrawal period assignment for the combination of Stafac® and Monteban™ in Type C medicated feed with virginiamycin at 20 g/ton and narasin at up to 90 g/ton, because the narasin concentration used in the study was only 73 g/ton, below 90 g/ton.

The sponsor did not conduct additional tissue residue depletion studies to support this approval. CVM relied on the tissue residue depletion study No. V-M-4021-83 discussed above, and the residue chemistry information contained in the NADA 118-980 file for Monteban™ to reach the conclusion that the combination of Stafac® and Monteban™ in Type C medicated feed with virginiamycin at 20 g/ton and narasin at up to 90 g/ton also qualifies for a zero-day withdrawal period assignment. CVM's rationale for the conclusion is summarized below:

- Monteban™ (narasin Type A medicated article, NADA 118-980) initially was approved for use alone in Type C medicated feed for broiler chickens at the dose of up to 72 g narasin/ton. A zero-day withdrawal period was assigned for the approval (FOI Summary for the original approval dated August 14, 1986). The results of the tissue residue depletion study No. S-AAC 8408 (NADA 118-980) in support of the approval showed that, at the practical zero withdrawal, the parent narasin residue concentrations in the abdominal fat samples of chickens treated with narasin alone at 72 g/ton in Type C medicated feed ranged from 25 to 180 ppb. The calculated 99th percentile upper tolerance limit with 95% confidence was 307 ppb, below the codified tolerance of 480 ppb for parent narasin in chicken abdominal fat (FOI Summary for the supplemental approval dated April 11, 2001).

- The results of the sponsor's tissue residue depletion study No. V-M-4021-83 described above showed that, at the practical zero withdrawal, the parent narasin residue concentrations (a calculated 99th percentile upper tolerance limit with 95% confidence of 54 ppb) in the skin/fat samples from the chickens treated with the combination of

virginiamycin at 20 g/ton and narasin at 73 g/ton in Type C medicated feed did not exceed the parent narasin residue concentrations in the abdominal fat samples from the chickens treated with narasin alone at 72 g/ton (study No. S-AAC 8408).

- Monteban™ (narasin Type A medicated article; NADA 118-980) currently is approved for use alone at up to 90 g narasin/ton in Type C medicated feed for broiler chickens. A zero-day withdrawal period is assigned for the approval (FOI Summary for the supplemental approval dated March 2, 2012).

- The data from the studies No. S-AAC 8408 and No. V-M-4021-83 showed that, when virginiamycin was used at 20 g/ton with narasin at 73 g/ton in Type C medicated feed, the presence of virginiamycin in the feed does not cause narasin residue concentrations in the animals treated with the combination to be above those in the animals treated with narasin alone at 72 g/ton in the feed.

- As such, when virginiamycin is used at 20 g/ton in combination with narasin at up to 90 g/ton in the feed for broiler chickens, which is the use condition of this approval, CVM found it unlikely that the presence of virginiamycin in the feed will cause narasin residue concentrations in the animals treated with the combination to be above those in the animals treated with narasin alone at up to 90 g/ton.

Conclusions: The data from Study V-M-4021-83 and the residue chemistry information in the NADA 118-980 file, as summarized above, support a zero-day withdrawal period assignment for the combination of virginiamycin (20 g/ton) and narasin (54 to 90 g/ton) in Type C medicated feed for use in 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).

3. Tolerances

   A tolerance for virginiamycin in edible tissues (excluding eggs) of chickens is not required (21 CFR §556.750).

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

4. Withdrawal Period

A zero-day withdrawal period is assigned for the combination of virginiamycin (20 g/ton) and narasin (54 to 90 g/ton) in Type C medicated feed for use in broiler chickens.

D. 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).

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).

3. Availability of Method

   The validated analytical method for analysis of residues of narasin 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.

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 Monteban™ 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 Monteban™ 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.