Date of Approval: January 13, 2017

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-472

Clinacox® and Stafac®

diclazuril and virginiamycin

Type A Medicated Articles to be Used in the Manufacture of Type C Medicated Feeds

Broiler Chickens

For the prevention of coccidiosis caused by *Eimeria tenella E. necatrix, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima*. Because diclazuril is effective against *E. maxima* late in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesions scores and improve performance and health of birds challenged with *E. maxima*. For prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin in broiler chickens.

Sponsored by:

Huvepharma EOOD

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I. GENERAL INFORMATION

A. File Number

NADA 141-472

B. Sponsor

Huvepharma EOOD
5th Floor
3A Nikolay Haytov Str.
1113 Sofia, Bulgaria

Drug Labeler Code: 016592

U.S. Agent:
Kelly W. Beers, Ph.D.
525 Westpark Drive, Suite 230
Peachtree City, GA 30269

C. Proprietary Names

Clinacox® and Stafac®

D. Established Names

Diclazuril and virginiamycin

E. Pharmacological Category

Diclazuril: anticoccidial
Virginiamycin: antimicrobial

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]

Diclazuril: 0.2% diclazuril
Virginiamycin: 20, 50, or 227 g/lb. virginiamycin

[1] The sponsors of these individual currently marketed Type A medicated articles may have approvals for other strengths of these products 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 is the subject of this approval.

H. How Supplied

Diclazuril: 50 lb. bag
Virginiamycin (Stafac® 20 and Stafac® 50): 50 lb. bag
Virginiamycin (Stafac® 500): 55 lb. (25 kg), 1322 lb. (600 kg), or 1764 lb. (800 kg) bag

I. Dispensing Status

VFD

J. Dosage Regimen

Feed 0.91 grams (1 ppm) diclazuril and 20 grams virginiamycin per ton of Type C medicated feed. Feed continuously as the sole ration.

K. Route of Administration

Oral

L. Species/Class

Broiler chickens

M. Indications

For the prevention of coccidiosis caused by *Eimeria tenella E. necatrix, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima*. Because diclazuril is effective against *E. maxima* late in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesions scores and improve performance and health of birds challenged with *E. maxima*. For prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin in broiler chickens.

II. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Animal Drug Availability Act (ADAA) of 1996, if the animal drugs or active ingredients intended for use in combination in an animal feed have already been separately approved for the particular uses and conditions for which they are intended for use in combination, the Center for Veterinary Medicine (CVM) will not refuse to approve an NADA for the combination on effectiveness grounds unless the FDA finds that the sponsor fails to demonstrate that:

- 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.

Diclazuril, as provided by Huvepharma EOOD, have previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima* (21 CFR §558.198(d)(1)(i)). Virginiamycin, as provided by Phibro Animal Health Corp., has previously been separately approved for use in feed for broiler chickens for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin (21 CFR §558.635(e)(1)(xiii)). Effectiveness of each drug, diclazuril and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma EOOD's approved NADA 140-951 for diclazuril and Phibro Animal Health Corp.'s approved NADA 091-467 for virginiamycin to which Huvepharma EOOD has right of reference.

Because diclazuril plus virginiamycin each has at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that diclazuril and virginiamycin provide appropriate concurrent use for the intended target population. The use of diclazuril plus virginiamycin provides appropriate concurrent use because these drugs are intended to treat different conditions (prevention of coccidiosis and prevention of necrotic enteritis caused by *Clostridium perfringens*) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed.

III. TARGET ANIMAL SAFETY

In accordance with the FD&C Act, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on target animal safety grounds unless:

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and CVM finds that the application fails to show that the combination is safe, or
- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and CVM finds that the application fails to show that the combination is safe.

Diclazuril, as provided by Huvepharma EOOD, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima* (21 CFR §558.198(d)(1)(i)). Virginiamycin, as provided by Phibro Animal Health Corp., has previously been separately approved for use in feed for broiler chickens for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin (21 CFR §558.635(e)(1)(xiii)).

Under the provisions of ADAA, this original approval allows for the combination of diclazuril (as provided by Huvepharma EOOD) and virginiamycin (as provided by Phibro Animal Health Corp.). Target animal safety for each drug, diclazuril and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma EOOD's approved NADA 140-951 for diclazuril and Phibro Animal Health Corp.'s approved NADA 091-467 for virginiamycin to which Huvepharma EOOD has right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of diclazuril and virginiamycin when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Therefore, in accordance with the FD&C Act, as amended by the ADAA of 1996, no specific target animal safety studies are required for approval of this application.

IV. HUMAN FOOD SAFETY

In accordance with the FD&C Act, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM finds that the application fails to establish that:

- 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, or
- 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. Toxicology

Safety of the individual drugs in this combination product has been established by data in NADA 140-951 for diclazuril (FOI Summary dated April 21, 1999) and NADA 091-467 for virginiamycin (46 FR 18966, dated March 27, 1981).

B. 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 140-951 (FOI Summary dated April 21, 1999) contains summaries of studies supporting the approval of diclazuril in broiler chickens. NADA 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981).

   b. Comparative Metabolism Study

      CVM did not require comparative metabolism studies for this approval.

NADA 140-951 (FOI Summary dated April 21, 1999) contains summaries of studies supporting the approval of diclazuril in broiler chickens. NADA 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981).

c. Tissue Residue Depletion Study

(1) Tissue Residue Non-Interference Study in Broiler Poultry Medicated with Virginiamycin in Combination with Diclazuril and Roxarsone[2], Study No. V-M-4052-92

Study Dates: October 1992 to October 1993.

Study Location: Las Cruces, NM

Study Design: The Study was conducted according to GLP.

Twelve two-day-old broiler chicks, equally mixed as to sex, were fed a medicated diet containing 1 ppm diclazuril and 45.4 g/ton roxarsone. On study day 20, 20 g/ton ^{14}C-virginiamycin was added to the medicated feed. Birds were fed the three-way combination until day 48, when the birds were sacrificed at six hours (practical zero withdrawal) after feed removal.

The tissues of birds were assayed for total residues by combustion and liquid scintillation counting. The results of the assays are given in the table below.

Table 1. Total Radioactive Residues (TRR, in ppm equivalents) in Liver, Muscle, and Skin with Adhering Fat.

Group	Gender	TRR (ppm eq.)[a]
Liver	Male	0.130
Liver	Female	0.134
Muscle	Male	0.013
Muscle	Female	< LOD
Skin/fat	Male	< LOD
Skin/fat	Female	< LOD

[a]Sample size: six birds
LOD (ppm) liver, muscle: 0.007
LOD (ppm) skin/fat: 0.013

(2) SCH 209203 (Diclazuril): Tissue Residue Depletion Study for

[2] Approval of the roxarsone Type A medicated article, 3-NITRO, has been previously withdrawn (78 FR 70062, dated November 22, 2013). After evaluation of the tissue residue interference study, it was determined that the data from the study for the three-way combination (virginiamycin at 20 g/ton, roxarsone at 45.4 g/ton, and diclazuril at 1 ppm) could be used to support assay noninterference and a zero-day withdrawal assignment for the two-way combination (virginiamycin at 20 g/ton and diclazuril at 1 ppm).

Diclazuril and Virginiamycin in Broiler Chickens, Study Number 97499

Study Dates: December 1997 to July 1998

Study Location: Lafayette, IN

Study Design: The Study was conducted according to GLP.

Birds were reared in floor pens from one day of age to day 43 of the study. Treatments were randomly assigned to pens. Pens contained 20 birds each. Two pens of each gender were fed the blank control feed, diclazuril at 1 ppm, or the drug combination (1 ppm diclazuril and 20 g/ton of virginiamycin) continuously. Tissue samples were collected on day 43. Three pooled liver samples, each of which represented three birds, from each pen were assayed. For this study, the GC-EC method was used to assay for the presence of diclazuril. No samples were collected for virginiamycin assay. The results are presented in the table below.

Table 2. Residue Concentrations in Chicken Liver.

Group	Gender	Diclazuril (ppm)[a]
Control	Male	< LOQ[b]
Control	Female	< LOQ
Diclazuril	Male	0.275
Diclazuril	Female	0.216
Diclazuril + Virginiamycin	Male	0.274
Diclazuril + Virginiamycin	Female	0.290

[a]Mean of six pooled liver samples: each pooled sample represents three birds
[b]The average of one pen was not quantifiable; the average of the other pen was 0.016 ppm
LOQ = 0.010 ppm

In conjunction with Study 97499, a liver sample from a control bird was spiked with diclazuril plus virginiamycin and assayed by GC-ECD for diclazuril. The results indicated that the presence of virginiamycin does not interfere with the diclazuril assay. A demonstration of diclazuril interference with the virginiamycin assay was not necessary because the requirement of a regulatory method to monitor tissue residues of virginiamycin in edible tissues was waived under NADA 091-467 (46 FR 18966, dated March 27, 1981).

2. Target Tissue and Marker Residue Assignment

No reassessments of target tissue and marker residue were needed for this approval. The marker residue for diclazuril in chickens is parent diclazuril. A specific target tissue is not identified (21 CFR §556.185). A target tissue and marker residue has not been established for virginiamycin.

3. Tolerance Assignments

   Tolerances for parent diclazuril (the marker residue) in chickens are as follows: 3 ppm in liver, 0.5 ppm in muscle, 1 ppm in skin with adhering fat (21 CFR §556.185). A tolerance for residues of virginiamycin in chickens is not required (21 CFR §556.750).

4. Withdrawal Period

   Study V-M-4052-92 showed that total residues of virginiamycin in all edible tissues of chickens were well below the respective safe concentrations at practical zero withdrawal. Study 97499 demonstrated that residues of parent diclazuril in liver were at least one order of magnitude below the applicable tolerance. The results of these studies support the use of the two-way combination of diclazuril and virginiamycin in broiler chicken feeds with no requirement of a withdrawal period.

C. Microbial Food Safety

1. Antimicrobial Resistance

   With respect to the human food safety evaluation for these types of combination new animal drug approvals, the Agency is permitted only to evaluate 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, we did not assess the impact of this combination of diclazuril and virginiamycin on antimicrobial resistance development among bacteria of public health concern in or on treated broiler chickens.

2. Impact of Residues on Human Intestinal Flora

   With respect to the human food safety evaluation for these types of combination new animal drug approvals, the Agency is permitted only to evaluate 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, we did not assess the impact of this combination of diclazuril and virginiamycin on the residues of diclazuril and virginiamycin in edible food products from broiler chickens on human intestinal flora and the need to establish a microbiological acceptable daily intake.

D. Analytical Method for Residues

The FOI Summary for the original approval of NADA 140-951 dated April 21, 1999, contains the analytical method summary for diclazuril in chickens. The requirement of a regulatory method to monitor tissue residues of

virginiamycin in edible tissues was waived under NADA 091-467 (46 FR 18966, dated March 27, 1981). The method for diclazuril is available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY

The product labeling contains no information regarding safety to humans handling, administering, or exposed to the Type C medicated feed.

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 Clinacox® and Stafac® demonstrate that, when used according to the label, they are safe and effective for the prevention of coccidiosis caused by *Eimeria tenella E. necatrix, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima* and for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin in broiler chickens. Additionally, data demonstrate that residues in food products derived from broiler chickens treated with Clinacox® and Stafac® will not represent a public health concern when the product 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.

Labeling restricts this drug to use under the professional supervision of a licensed veterinarian. The decision to restrict this drug to use by or upon a lawful VFD issued by a licensed veterinarian was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately and safely use this product and (b) restricting this drug to use by or upon a lawful VFD issued by a licensed veterinarian should help prevent indiscriminate use, which could result in violative tissue residues.

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.