Date of Approval: October 27, 2017

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-467

Inteprity™ and Monteban™

avilamycin and narasin

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

Broiler chickens

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

Sponsored by:

Elanco US Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-467

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Inteprity™ and Monteban™

D. Established Name

avilamycin and narasin

E. Pharmacological Category

Avilamycin: antimicrobial
Narasin: 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]

Avilamycin: 45.4 g/lb avilamycin
Narasin: 45 g/lb narasin

H. How Supplied

Avilamycin: 55.12 lb bag
Narasin: 55.12 lb bag

I. Dispensing Status

VFD

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[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 are the subject of this approval.

J. Dosage Regimen

13.6 to 40.9 g/ton avilamycin and 54 to 90 g/ton narasin per ton of Type C medicated feed, to be fed as the sole ration for 21 consecutive days.

K. Route of Administration

Oral

L. Species/Class

Broiler chickens

M. Indication

For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens;* and for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima* 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.

Avilamycin, as provided by Elanco US Inc., has previously been separately approved for use in feed for broiler chickens for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* (21 CFR 558.68). Narasin, as provided by Elanco US Inc., has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima* (21 CFR 558.363). Effectiveness of each drug, avilamycin and narasin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco US Inc.'s approved NADAs 141-439 and 118-980 for avilamycin and narasin, respectively.

Because avilamycin and narasin each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that avilamycin plus narasin provide appropriate concurrent use for the intended target population. The use of avilamycin plus narasin provides appropriate concurrent use because these drugs are intended to treat different conditions (prevention of mortality caused by necrotic enteritis and prevention of coccidiosis, respectively) 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.

Avilamycin, as provided by Elanco US Inc., has previously been separately approved for use in feed for broiler chickens for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* (21 CFR 558.68). Narasin, as provided by Elanco US Inc., has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima* (21 CFR 558.363).

Under the provisions of ADAA, this original approval allows for the combination of avilamycin (as provided by Elanco US Inc.) and narasin (as provided by Elanco US Inc.). Target animal safety for each drug, avilamycin and narasin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco US Inc.'s approved NADAs 141-439 and 118-980 for avilamycin and narasin, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of avilamycin and narasin 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 141-438 for avilamycin (FOI Summary dated May 8, 2015), and NADA 118-980 for narasin (FOI Summaries dated August 14, 1986 and April 11, 2001).

B. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Residue Depletion Study

   Title: Non-Clinical Laboratory Study (GLP): Residue Noninterference in Chickens Following Oral Administration of Avilamycin in Combination with Monteban™ and Maxiban® in the Feed (Study No. 014-01414)

   Study Completion Date: April 7, 2016

   Study Location: In-life phase – Las Cruces, NM; Analytical phase – Greenfield, IN

   Objective: The objective of this GLP study was to confirm that residues of narasin in fat of broiler chickens following administration of avilamycin and narasin (Monteban™) are below the codified tolerances at 0 days.

   The control group had 30 males and 30 females. The treatment group had 10 males and 10 females. The control birds were fed basal Type C nonmedicated ration for 38 days and then were slaughtered. The treated birds were fed nonmedicated ration for 12 days and then medicated feed for 28 days. Treated birds were slaughtered after a 6-hour practical zero withdrawal. Abdominal fat was collected from the control and treated groups. The tissue samples were analyzed with LC-MS/MS to determine the concentration of narasin. Demonstration of noninterference with the analytical method was not needed due to the dissimilar chemical structures of avilamycin and narasin. Residues of narasin in abdominal fat of chickens fed avilamycin and narasin ranged from 18.9 to 101 ppb.

2. Target Tissue and Marker Residue Assignment

No reassessments of target tissue and marker residue were needed for this approval. Neither a target tissue nor a marker residue is codified for avilamycin in

chickens. The marker residue for narasin is parent drug and the target tissue in chickens is abdominal fat (NADA 118-980 dated April 11, 2001).

3. Tolerance Assignments

   A tolerance for residues of avilamycin in chickens is not required (21 CFR 556.68). The tolerance for narasin is 480 ppb in chicken abdominal fat (21 CFR 556.428).

4. Withdrawal Period

   A 0-day withdrawal period is assigned.

C. Microbial Food Safety

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 1) assess the impact of this combination of avilamycin and narasin on antimicrobial resistance among bacteria of public health concern in or on treated broiler chickens, or 2) assess the impact of residues of avilamycin and narasin in edible food products from treated broiler chickens on human intestinal flora.

D. Analytical Method for Narasin Residues

1. Description of Analytical Method

   An analytical method for narasin in chicken tissues has been published, based on LC-MS/MS.

2. Availability of Method

   The method is published in the following reference:

   Lombardi, K.R., Burnett, T.J., Brunelle, S.L., Ulrey, W.D., and Coleman, M.R. Determination and confirmation of narasin and monensin in chicken, swine, and bovine tissues by LC/MS/MS: Final Action 2011.24. Journal of AOAC International Vol. 96, No 4 (2013).

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type C medicated feed:

Not for use in humans. 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 Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data contained in the previously approved NADAs for Inteprity™ and Monteban™ demonstrate that, when they are used according to the label, they are safe and effective for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens;* 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 treated with Inteprity™ and Monteban™ 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 Federal Food, Drug, and Cosmetic 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.