Date of Approval: January 28, 2020

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-466

Inteprity™ and Maxiban™

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

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

Broiler chickens

Supplemental approval of an Animal Drug Availability Act of 1996 (ADAA) feed combination to provide for 1) a change in the broiler chicken age restriction caution statement from 10 days to 18 days of age as follows: To assure responsible antimicrobial drug use in broiler chickens, treatment administration must begin on or before 18 days of age; and, 2) an update to the withdrawal periods and residue warnings statement as follows: No withdrawal period is required when used according to labeling. Do not feed to chickens producing eggs for human consumption.

Sponsored by:

Elanco US Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-466

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Names

Inteprity™ and Maxiban™

D. Drug Product Established Names

avilamycin Type A medicated article and narasin and nicarbazin Type A medicated article

E. Pharmacological Categories

Inteprity™: 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]

Inteprity™: 45.4 g/lb of avilamycin
Maxiban™: 36 g/lb of narasin and 36 g/lb of nicarbazin (1:1 ratio)[2]

H. How Supplied

Inteprity™: 55.12 lb bag
Maxiban™: 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 that are for use in the same species and class, for the same indications, and at the same dosages, but are not currently marketing those strengths of these Type A medicated articles. Such strengths, when legally marketed, are also approved for use in the manufacture of Type C medicated feeds that are the subject of this approval.
[2] Narasin and nicarbazin may only be sourced from Maxiban™, NADA 138-952, which provides these two drugs at a 1:1 ratio.

J. Route of Administration

Oral

K. Species/Class

Broiler chickens

L. Indication and Dosage Regimen

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

a. 13.6 to 40.9 g/ton of avilamycin (as Inteprity™) for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*.

b. 27 to 45 g/ton each of narasin and nicarbazin (as Maxiban™) for the prevention of coccidiosis by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati*, and *E. maxima*.

Feed as the sole ration for 21 consecutive days.

M. Effect of Supplement

This supplement approval provides for 1) a change in the broiler chicken age restriction caution statement from 10 days to 18 days of age as follows: To assure responsible antimicrobial drug use in broiler chickens, treatment administration must begin on or before 18 days of age; and, 2) an update to the withdrawal periods and residue warnings statement as follows: No withdrawal period is required when used according to labeling. Do not feed to chickens producing eggs for human consumption.

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the ADAA of 1996, allows for drugs to be fed in combination in or on medicated feed without additional demonstration of their effectiveness or target animal safety when certain conditions are met. In those cases, the FD&C Act provides that effectiveness and target animal safety of each drug, demonstrated in its NADA at the time of the approval, are adequate. The Agency has based its determination of the effectiveness and target animal safety of the combination of avilamycin Type A medicated article and narasin and nicarbazin Type A medicated article on the effectiveness and target animal safety of the previously separately approved conditions of use for Inteprity™ and Maxiban™ for use in broiler chickens, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness;

- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population;
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness;
- there was not a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that was not adequately evaluated based on the information contained in the application for the combination, and no data presented in the application raised a safety concern with the Agency; and
- there was not a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and no data presented in the application raised a safety concern with the Agency.

Effectiveness and target animal safety of the individual drugs in this combination product has been established by data in the following NADAs (see Table II.1):

Table II.1. Summary of effectiveness and target animal safety for the individual drugs subject to this combination approval.

Drug Product	Indications	Approval Information
Inteprity™ Sponsored by Elanco US Inc.	For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens.	NADA 141-439 (refer to the FOI Summary, dated May 2, 2016)
Maxiban™ Sponsored by Elanco US Inc.	For the prevention of coccidiosis in broiler chickens 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)

III. HUMAN FOOD SAFETY

The human food safety of each drug was adequately demonstrated in its NADA at the time of the approval. In general, this means that additional microbial food safety and toxicology data were not needed; however, additional residue chemistry data were needed for residue depletion and assay noninterference for the combination product. The Agency has based its determination of the human food safety of the combination of avilamycin, narasin, and nicarbazin on the human food safety of the previously separately approved conditions of use for Inteprity™ and Maxiban™ for use in broiler chickens, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, and

- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Microbial Food Safety

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 Federal Food, Drug, and Cosmetic Act]. Therefore, the effects of this combination of Inteprity™ and Maxiban™ on antimicrobial resistance development among bacteria of public health concern in or on treated broiler chickens was not assessed.

B. Toxicology

CVM did not require toxicology studies for this supplemental approval. Safety of the individual drugs in this combination product has been established by data in the following NADAs (see Table III.1):

Table III.1. Toxicology assessment of individual drugs in this combination product.

Drug Product	Approval Information
Avilamycin	NADA 141-438 (refer to the FOI Summary, dated May 8, 2015)
Narasin	NADA 118-980 (refer to the FOI Summaries, dated August 14, 1986, and April 11, 2001)
Nicarbazin	NADA 135-468 (as published in the FEDERAL REGISTER (vol. 50 FR 13561), on April 5, 1985) NADA 138-952 (refer to the FOI Summary, dated July 11, 2018)

C. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-466 dated October 27, 2017, contains a summary of residue chemistry studies for broiler chickens. Based on

the results from the total residue and metabolism study (Study No. 805129), a tolerance of 52 ppm for 4,4'-dinitrocarbanilide (DNC)[3] in chicken liver was calculated (21 CFR 556.445).

This supplement results in a change to the previously established withdrawal period for Maxiban™. The withdrawal period is zero days. Refer to the FOI Summary for the supplemental approval of NADA 138-952, dated July 11, 2018.

This supplement does not result in any change to the previously established withdrawal period for Inteprity™. The withdrawal period remains zero days. Refer to the FOI Summary for the original approval of NADA 141-439, dated May 2, 2016.

The withdrawal period for this combination product is zero days.

D. Analytical Method for Residues

The FOI Summary for the original approval of NADA 141-466 dated October 27, 2017, contains the analytical method summary for DNC and narasin in chicken tissues. Because a tolerance has not been assigned for residues of avilamycin in chicken tissues, a validated analytical method for avilamycin is not needed.

The validated analytical methods for analysis of residues of DNC and narasin 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 method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm

IV. USER SAFETY

CVM did not require user safety studies for this supplemental approval.

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. To report adverse effects in users, to obtain more information, or to obtain a Safety Data Sheet, call 1-800-428-4441.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the FD&C Act and 21 CFR part 514. The data contained in the previously approved NADAs for Inteprity™ and Maxiban™ 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

[3] Nicarbazin is an equimolar complex consisting of N,N'-Bis-(4 nitrophenyl) urea or 4,4'-dinitrocarbanilide (DNC), and 4,6-dimethylpyrimidine-2-one, also known as 2-hydroxy-4,6-dimethylpyrimidine (HDP).

food products derived from chickens administered Inteprity™ 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 issues by a licensed veterinarian in the course of their professional practice. In addition, the veterinary feed directives issues 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 because 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)(iii) of the FD&C Act.

C. Supplemental Applications

This supplemental approval did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(1)).

D. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.