Date of Approval: April 7, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-588

Rumensin™ and V-Max®

(monensin Type A medicated article) and (virginiamycin)

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

growing beef steers and heifers fed in confinement for slaughter

Original approval of an Animal Drug Availability Act of 1996 (ADAA) feed combination for the indications listed in Section I.L.

Sponsored by:

Phibro Animal Health Corp.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-588

B. Sponsor

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

Drug Labeler Code: 066104

C. Proprietary Names

Rumensin™ and V-Max®

D. Drug Product Established Names

monensin Type A medicated article and virginiamycin

E. Pharmacological Categories

Rumensin™: ionophore/anticoccidial
V-Max®: antimicrobial

F. Dosage Form

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

G. Amount of Active Ingredients in Currently Marketed Products[1]

Rumensin™: 90.7 g/lb of monensin USP
V-Max®: 50 g/lb and 227 g/lb of virginiamycin

H. How Supplied

Rumensin™: 25 kg, 600 kg, and 900 kg bags
V-Max®: 50 lb, 55 lb, 100 lb, and 1322 lb bags

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 B and Type C medicated feeds that are the subject of this approval.

K. Species/Classes

Cattle/growing beef steers and heifers fed in confinement for slaughter

L. Indications and Dosage Regimens

1. For the prevention and control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii,* and reduction of incidence of liver abscesses in growing beef steers and heifers fed in confinement for slaughter.

    a. 10 to 40 g/ton of monensin (as Rumensin™) to provide 0.14 to 0.42 mg/lb body weight per day, depending on the severity of coccidiosis challenge, up to 480 mg/head/day of monensin for the prevention and control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii*.

    b. 13.5 to 16 g/ton of virginiamycin (as V-Max®) to provide 85 to 240 mg/head/day of virginiamycin for the reduction of incidence of liver abscesses.

    Feed at every feeding.

2. For improved feed efficiency and reduction of incidence of liver abscesses in growing beef steers and heifers fed in confinement for slaughter.

    a. 5 to 40 g/ton of monensin (as Rumensin™) to provide 50 to 480 mg/head/day of monensin for improved feed efficiency.

    b. 13.5 to 16 g/ton of virginiamycin (as V-Max®) to provide 85 to 240 mg/head/day of virginiamycin for the reduction of incidence of liver abscesses.

    Feed at every feeding.

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 monensin Type A medicated article and virginiamycin on the effectiveness and target animal safety of the previously separately approved conditions of use for Rumensin™ and V-Max® for use in growing beef steers and heifers fed in confinement for slaughter, 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 has been established by data in the following NADAs (refer to Table II.1):

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

Drug Product	Indications	Approval Information
Rumensin™* Sponsored by Elanco US Inc.	1. For use in feeds for growing beef steers and heifers fed in confinement for slaughter for improved feed efficiency. 2. For use in feeds for growing beef steers and heifers fed in confinement for slaughter for the prevention and control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii.*	NADA 095-735 (refer to the FOI Summary, dated December 1, 2006)
V-Max® Sponsored by Phibro Animal Health Corp.	For use in feeds for cattle fed in confinement for slaughter for reduction of incidence of liver abscesses.	NADA 140-998 (refer to the FOI Summary, dated June 24, 1994)

*Elanco US Inc. has provided Phibro Animal Health Corp. right of reference to use Rumensin™ in this combination.

III. 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 monensin and virginiamycin on the human food safety of the previously separately approved conditions of use for Rumensin™ and V-Max® for use in growing beef steers and heifers fed in confinement for slaughter, 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 the Center for Veterinary Medicine's (CVM) 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 III.1. Toxicology assessment of the individual drugs in this combination.

Drug Product	Approval Information
Rumensin™	NADA 095-735 (refer to the FOI Summaries, dated August 9, 1989, December 16, 1998, October 28, 2004, and December 1, 2006)

Drug Product	Approval Information
V-Max®	NADA 140-998 (refer to the FOI Summary, dated June 24, 1994) NADA 091-467 (as published in the FEDERAL REGISTER (46 FR 18966) on March 27, 1981)

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 095-735 (as published in the FEDERAL REGISTER (40 FR 58289) on December 16, 1975, and FOI Summary dated October 28, 2004) contains summaries of studies supporting the approval of monensin in cattle. NADA 140-998 (FOI Summary, dated June 24, 1994) contains summaries of studies supporting the approval of virginiamycin in cattle.

   b. Comparative Metabolism Studies

   CVM did not require comparative metabolism studies for this approval. NADA 095-735 (as published in the FEDERAL REGISTER (40 FR 58289) on December 16, 1975, and FOI Summary dated October 28, 2004) contains summaries of studies supporting the approval of monensin in cattle. NADA 140-998 (FOI Summary, dated June 24, 1994) contains summaries of studies supporting the approval of virginiamycin in cattle.

   c. Residue Depletion Study

   Study Number: USD169-499

   Study Dates: June 2022 to December 2023

   Study Location: Parma, ID

   Study Design:

   Objective: The objective of this Good Laboratory Practice (GLP) single timepoint residue noninterference study was to evaluate tissue residue concentrations in cattle liver and noninterference of virginiamycin in combination with monensin, ractopamine, and lubabegron, when administered orally in the feed.

Dosing: Twenty-two growing cattle weighing 249 kg (548 lb.) to 333 kg (733 lb.) were used for the study. Animals were randomized to one of three treatment groups as described in Table III.2. The two control animals were slaughtered before the acclimation phase. Cattle being treated with monensin received the lower dose of monensin (30 g/ton) during a 14-day acclimation phase, and then increased to the higher dose (40 g/ton) during the 15-day treatment phase. During the treatment phase, animals were provided a Type C medicated feed containing lubabegron, ractopamine hydrochloride, monensin, and virginiamycin.

Table III.2. Treatment Groups (TG) and Feed Dosage.

TG	Lubabegron Target Dose (g/ton)	Ractopamine Target Dose (g/ton)	Monensin Target Dose (g/ton)	Virginiamycin Target Dose (g/ton)	Number of Animals*
01	0	0	0	0	1M; 1F
02	0	24.6	40	16	5M; 5F
03	4.54	0	40	16	5M; 5F

* M = male; F = female

Cattle were removed from medicated feed approximately 10 to 12 hours prior to slaughter. Animals were slaughtered and liver tissue was collected from all treatment groups. Liver tissue was analyzed for the concentration of, lubabegron using the official method G1886 Rev 4.0 (2020), ractopamine using Food Safety and Inspection Service (FSIS) method CLG-RAC1.01, and monensin using an AOAC International official method 2011.24. Liver samples from TG02 animals were analyzed for monensin and ractopamine. Liver samples from TG03 animals were analyzed for monensin and lubabegron. No tissue was tested for virginiamycin because a tolerance for residues is not required. Liver tissues from the control group (TG01) were processed after all other samples.

Results: The results of analysis of ractopamine, lubabegron, and monensin are shown in Table III.3. All animals had residue concentrations for ractopamine, lubabegron, and monensin that were below their respective tolerances in all treatment groups. Control liver samples from TG01 animals were below the limit of quantitation (LOQ) for monensin, ractopamine, and lubabegron.

Table III.3. Mean Residue Concentrations for Ractopamine, Lubabegron and Monensin

Treatment Group	Ractopamine in Liver (parts per billion (ppb))	Lubabegron in Liver (ppb)	Monensin in Liver (ppb)
02	< LOQ	NA	28.6
03	NA	2.19	19.5

NA: Not Applicable
Ractopamine assay LOQ = 25 ppb
Lubabegron assay LOQ = 1 ppb
Monensin assay LOQ = 0.6 ppb

d. Method Noninterference Study

Study Number: EFII-211252

Study Dates: April 2022 to November 2022

Study Location: Indianapolis, IN

Study Design:

Objective: The objective of this GLP study was to demonstrate analytical method noninterference for lubabegron, monensin, ractopamine, and virginiamycin in the analytical methods for ractopamine, lubabegron, and monensin.

Experimental Design: Control cattle liver tissue was fortified with lubabegron, monensin, ractopamine, and virginiamycin. These samples were then analyzed for ractopamine using the Official Method CLG-RAC1.01, for lubabegron using the Official Method G1886 Rev 4.0 (2020), and for monensin using the AOAC International Official Method 2011.24 method.

Results: The percent recoveries for all groups were within acceptable ranges for their respective methods and concentrations, and the percent coefficient of variation (%CV) for all groups in all assays was < 10%. Ractopamine, lubabegron, monensin, and virginiamycin do not interfere with the detection of lubabegron, monensin, and ractopamine.

2. Target Tissues and Marker Residues

No reassessments for target tissues and marker residues were needed for this approval.

Neither a target tissue nor a marker residue is codified for monensin or virginiamycin in cattle.

3. Tolerances

   Tolerances for monensin in cattle are as follows: 0.10 parts per million (ppm) in liver, 0.05 ppm in muscle, kidney, and fat (21 CFR 556.420).

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

4. Withdrawal Period

   Results from study USD169-499 summarized above showed that residues of monensin in cattle tissues were below their respective tolerances at 0-day withdrawal. The data support assignment of a 0-day withdrawal period for monensin dosed at 5 to 40 g/ton in combination with virginiamycin at 13.5 to 16 g/ton.

D. Analytical Method for Residues

1. Determinative Method

   The bioautographic method for determination of monensin in cattle tissues is described in NADA 095-735 (as published in the FEDERAL REGISTER (40 FR 58289) on December 16, 1975). A determinative method was not required for virginiamycin.

2. Confirmatory Method

   A confirmatory method was not required for monensin. However, the AOAC International Final Action liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for monensin was bridged to the official bioautographic method and is capable of confirming monensin in tissue samples. A confirmatory method was not required for virginiamycin.

3. Availability of Method

   The validated analytical method for analysis of residues of monensin 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.

IV. USER SAFETY

CVM did not require user safety studies for this approval.

There is no information regarding safety to humans handling, administering, or exposed to the Type B and C medicated feeds necessary on the combination labeling.

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 Rumensin™ and V-Max® demonstrate that, when they are used according to the label, they are safe and effective for the conditions of use in the General Information Section above. Additionally, data demonstrate that residues in food products derived from growing beef steers and heifers fed in confinement for slaughter administered Rumensin™ and V-Max® 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 veterinary feed directives 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 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 mitigate the potential for 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.