Date of Approval: April 8, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-587

Optaflexx™ and Rumensin™ and V-Max®

(ractopamine hydrochloride Type A medicated article) and (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.

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I. GENERAL INFORMATION

A. File Number

NADA 141-587

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

Optaflexx™ and Rumensin™ and V-Max®

D. Drug Product Established Names

ractopamine hydrochloride Type A medicated article and monensin Type A medicated article and virginiamycin

E. Pharmacological Categories

Optaflexx™: beta adrenergic agonist
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]

Optaflexx™: 45.4 g/lb of ractopamine hydrochloride
Rumensin™: 90.7 g/lb of monensin USP
V-Max®: 50 g/lb and 227 g/lb of virginiamycin

H. How Supplied

Optaflexx™: 25 lb bag
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)

[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.

J. Route of Administration

Oral

K. Species/Classes

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

L. Indications and Dosage Regimens

1. For increased rate of weight gain, improved feed efficiency, 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 during the last 28 to 42 days on feed.

    a. 8.2 to 24.6 g/ton of ractopamine hydrochloride (as Optaflexx™) to provide 70 to 430 mg/head/day of ractopamine hydrochloride for increased rate of weight gain and improved feed efficiency.

    b. 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*.

    c. 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 as a sole ration during the last 28 to 42 days on feed.

2. For increased rate of weight gain, improved feed efficiency, increased carcass leanness, 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 during the last 28 to 42 days on feed.

    a. 9.8 to 24.6 g/ton of ractopamine hydrochloride (as Optaflexx™) to provide 90 to 430 mg/head/day ractopamine hydrochloride for increased rate of weight gain, improved feed efficiency, and increased carcass leanness.

    b. 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*.

    c. 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 as a sole ration during the last 28 to 42 days on feed.

3. For increased rate of weight gain and improved feed efficiency, 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 during the last 28 to 42 days on feed when ractopamine hydrochloride is used as a top dress with rations containing monensin and virginiamycin.

a. 8.2 to 24.6 g/ton of ractopamine hydrochloride (as Optaflexx™) to provide 70 to 400 mg/head/day of ractopamine hydrochloride for increased rate of weight gain and improved feed efficiency.

b. 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*.

c. 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 a minimum of 1.0 lb per head per day of this Type C top-dress medicated feed during the last 28 to 42 days on feed.

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 ractopamine hydrochloride Type A medicated article, monensin Type A medicated article, and virginiamycin on the effectiveness and target animal safety of the previously separately approved conditions of use for Optaflexx™, 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
Optaflexx™* Sponsored by Elanco US Inc.	1. For use in complete feeds for cattle fed in confinement for slaughter during the last 28 to 42 days on feed for increased rate of weight gain, improved feed efficiency and increased carcass leanness. 2. For use in top dress feed for cattle fed in confinement for slaughter during the last 28 to 42 days on feed for increased rate of weight gain and improved feed efficiency.	NADA 141-221 (refer to the FOI Summary, dated June 13, 2003, for use in complete feeds, and the FOI Summary dated December 11, 2009, for use as a top dress)
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 Optaflexx™ and 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 ractopamine hydrochloride, monensin, and virginiamycin on the human food safety of the previously separately approved conditions of use for Optaflexx™, 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
Optaflexx™	NADA 141-221 (refer to the FOI Summary, dated June 13, 2003)
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 141-221 (FOI Summaries, dated June 13, 2003, and December 11, 2009) contains summaries of studies supporting the approval of ractopamine hydrochloride in cattle. 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 November 6, 2018) 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 141-221 (FOI Summaries, dated June 13, 2003, and December 11, 2009) contains summaries of studies supporting the approval of ractopamine hydrochloride in cattle. 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 November 6, 2018) 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 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.

The target tissue for ractopamine in cattle is liver and the marker residue is ractopamine (21 CFR 556.570).

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

3. Tolerances

   The tolerances for ractopamine in cattle are as follows: 0.09 parts per million (ppm) in liver, 0.03 ppm in muscle (21 CFR 556.570).

   Tolerances for monensin in cattle are as follows: 0.10 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 and/or Milk Discard Time, and/or Honey Discard Time

   Results from study USD169-499 summarized above showed that residues of ractopamine and monensin were below their respective tolerances at 0-day withdrawal. The data support assignment of a 0-day withdrawal period for ractopamine dosed at 8.2 to 24.6 g/ton in combination with monensin at 5 to 40 g/ton, and virginiamycin at 13.5 to 16 g/ton.

D. Analytical Methods for Residues

1. Determinative Method

   The high-performance liquid chromatography (HPLC) with fluorescence detection method for determination of ractopamine in cattle tissues is described in NADA 141-221 (FOI Summary, dated December 22, 1999). 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 ractopamine or virginiamycin.

3. Availability of Method

   The validated analytical methods for analysis of residues of ractopamine and monensin 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 approval.

The combination labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type B and C medicated feeds:

The active ingredient in Optaflexx™, ractopamine hydrochloride, is a beta-adrenergic agonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for use in humans. Keep out of reach of children. The Optaflexx™ formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling Optaflexx™, use protective clothing, impervious gloves, protective eye wear, and a NIOSH- approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse eyes thoroughly with water. If irritation persists, seek medical attention. The safety data sheet contains more detailed occupational safety information.

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 Optaflexx™, 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 Optaflexx™, 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.