Approval Date: January 27, 2004

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-225

Ractopamine Hydrochloride (OPTAFLEXX) plus Monensin Sodium (RUMENSIN)

1) (8.2 – 24.6 g ractopamine per ton of feed; 10 to 30 g monensin sodium per ton of feed) - Increased rate of weight gain, improved feed efficiency, and prevention and control of coccidiosis due to Eimeria bovis and E. zuernii in cattle fed in confinement for slaughter for the last 28 to 42 days on feed.

2) (9.8 – 24.6 g ractopamine per ton of feed; 10 to 30 g monensin sodium per ton of feed) - Increased rate of weight gain, improved feed efficiency, increased carcass leanness, and prevention and control of coccidiosis due to Eimeria bovis and E. zuernii in cattle fed in confinement for slaughter for the last 28 to 42 days on feed.

Sponsored By:

Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

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FREEDOM OF INFORMATION SUMMARY

OPTAFLEXX and RUMENSIN

for Cattle Fed in Confinement for Slaughter

1. GENERAL INFORMATION:

a. File Number:	NADA 141-225
b. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
c. Established Names:	Ractopamine hydrochloride plus Monensin sodium
d. Proprietary Names:	OPTAFLEXX and RUMENSIN
e. Dosage Form:	Type A medicated articles
f. How Supplied:	Ractopamine – 9 or 45 grams per pound as ractopamine hydrochloride Monensin – 20, 30, 45, 60, 80 and 90.7 grams per pound as monensin sodium
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Ractopamine hydrochloride – 45.4 grams per pound (100 grams per kilogram) Monensin sodium – 80 grams per pound
i. Route of Administration:	Oral in feed
j. Species/Class:	Cattle fed in confinement for slaughter
k. Recommended Dosage:	1) 8.2 to 24.6 g/ton ractopamine hydrochloride and 10 to 30 g/ton monensin sodium 2) 9.8 to 24.6 g/ton ractopamine hydrochloride and 10 to 30 g/ton monensin sodium
l. Pharmacological Category:	Beta adrenergic agonist and anticoccidial
m. Indications:	1) Increased rate of weight gain, improved

feed efficiency, and prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed.

2) Increased rate of weight gain, improved feed efficiency, increased carcass leanness, and prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed

2. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the animal drugs/ 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, FDA 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/drug intended only for the same use as another active ingredient/animal drug in 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/animal drug, there is a substantial evidence that each of the nontopical antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness

Ractopamine, as provided by Elanco Animal Health, has previously been separately approved for use in cattle for increased rate of weight gain, improved feed efficiency, and increased carcass leanness (in cattle fed in confinement for slaughter during the last 28 to 42 days on feed (21 CFR 558.500 (e)(2)). Monensin, as provided by Elanco Animal Health, has previously been separately approved (in a supplemental approval dated December 12, 2003) for use in cattle fed in confinement for slaughter for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* (21 CFR 558.355(f)(3)(vii)(a)). Effectiveness of each drug, ractopamine and monensin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 141-221 for ractopamine and NADA 95-735 for monensin.

Ractopamine and monensin are each intended for a different use therefore the NADA need not demonstrate, by substantial evidence, that ractopamine or monensin contributes to the labeled effectiveness of the combination. Ractopamine and monensin provide appropriate concurrent use

because these drugs are intended to treat different conditions likely to occur simultaneously in cattle fed in confinement for slaughter during the last 28 to 42 days on feed. (Ractopamine, for increased rate of weight gain, improved feed efficiency, and increased carcass leanness; and monensin, for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*;.)

3. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA 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 FDA 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 FDA finds that the application fails to show that the combination is safe.

Ractopamine, as provided by Elanco Animal Health, has previously been separately approved for use in cattle for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 28 to 42 days on feed (21 CFR 558.500(e)(2)). Monensin, as provided by Elanco Animal Health, has previously been separately approved (in a supplemental approval dated December 12, 2003) for use in cattle fed in confinement for slaughter for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* (21 CFR 558.355(f)(3)(vii)(a)).

Under the provisions of ADAA, this original approval allows for the combination of ractopamine and monensin (as provided by Elanco Animal Health). Target animal safety of each drug, ractopamine and monensin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADAs 141-221 and 95-735, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of ractopamine and monensin 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. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety studies are required for approval of NADA 141-225.

4. HUMAN SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients or intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human safety grounds unless FDA 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 drug in the combination.

A. Toxicity:

Safety for this combination product has been established by data in NADA 141-221 for ractopamine and NADA 95-735 for monensin.

B. Safe Concentrations of Total Residues – Calculation of the Acceptable Daily Intake (ADI) and the Safe Concentration:

The safe concentration for total residues of ractopamine hydrochloride are 0.25 ppm in muscle, 0.75 ppm in liver, and 1.5 ppm in kidney and fat. The acceptable daily intake (ADI) for total residues of ractopamine is 1.25 micrograms ractopamine hydrochloride per kilogram of body weight per day as codified under 21 CFR 556.570. The ADI for total residues of monensin is 12.5 milligrams per kilogram of body weight per day as codified under 21 CFR 556.420.

C. Tolerances and Withdrawal Time:

For ractopamine, a tolerance of 0.03 ppm is established for negligible residue of ractopamine in muscle and 0.09 ppm in liver of cattle as codified under 21 CFR 556.570. For monensin, a tolerance of 0.05 ppm is established for negligible residue of monensin in edible tissues of cattle as codified under 21 CFR 556.420. The tissue residue depletion data showed that residues of ractopamine hydrochloride, monensin, and tylosin were less than their respective tolerances at practical zero withdrawal, thereby supporting the assignment of a zero withdrawal period for the combination.

D. Residue Data:

D.1. Tissue Residue Non-Interference Study in Cattle Treated with Ractopamine, Monensin, Tylosin and Melengestrol Acetate. T4V699501

Investigator: J.W. Moran and J.M. Buck
Elanco Animal Health
2001 West Main St.
Greenfield, IN 46140

This study was conducted to determine non-interference in the tissue residue depletion in cattle of the ractopamine, monensin, tylosin and melengestrol acetate (MGA) combination. The cattle were fed medicated rations for 14.5 days. One treatment group of six cattle, three heifers and three steers, were fed 30 ppm ractopamine, 30 g/ton monensin, and 10 g/ton tylosin (RMT). A second treatment group of six heifers were fed 0.05 ppm MGA (0.5 mg/heifer/day) in addition to the combination of ractopamine, monensin, and tylosin (RMT+MGA). The animals were euthanized and tissues collected at practical zero withdrawal (12 hours). Liver tissue was collected and assayed for monensin and tylosin bioactive residues by microbiological methods, as well as assayed for ractopamine by high performance liquid chromatography with

fluorescence detection. Fat tissue was collected and assayed for MGA residue by gas chromatography with electron capture detection.

The ractopamine residues in the liver at practical zero-time withdrawal were 0.0074 ppm and 0.0041 ppm for the RMT and RMT+MGA treatments, which is below the tolerance established for cattle at 0.09 ppm. The monensin, tylosin and MGA residue levels found in this non-interference study at practical zero withdrawal were below the limit of quantitation of the respective methods of 0.04 ppm, 0.05 ppm, and 0.01 ppm, respectively. Since the assay values were below the limit of quantitation, it demonstrated that these three values were all below the approved tolerances for monensin, tylosin and MGA (0.05 ppm, 0.2 ppm, and 25 ppb, respectively).

These results indicate that the residue profiles of ractopamine, monensin, tylosin and melengestrol acetate are not altered when the drugs are fed in combination at the levels tested in this study.

Assay noninterference was tested by analyzing liver samples that had been fortified with 50 ppb monensin, 150 ppb ractopamine hydrochloride, 200 ppb tylosin, and 25 ppb MGA and comparing the results to those obtained from liver fortified with the single drug. The recovery data satisfactorily demonstrated assay noninterference.

The tissue residue depletion data showed that residues of ractopamine hydrochloride and monensin were less than their respective tolerances at practical zero withdrawal, thereby supporting the assignment of a zero withdrawal period for the combination.

E. Regulatory Methods for Residues:

The analytical methods for the determination of ractopamine and monensin in edible tissues are on file at the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

F. User Safety Concerns:

The following human warnings are found on the Type B and Type C medicated feed labeling:

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 the reach of children. The OPTAFLEXX 45 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 material safety data sheet contains more detailed occupational safety information. To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

5. *AGENCY CONCLUSIONS:*

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the FFDCA and 21 CFR Part 514 of the implementing regulations. Ractopamine and monensin when administered at 8.2 to 24.6 g/ton ractopamine hydrochloride and 10 to 30 g/ton monensin sodium are safe and effective for increased rate of weight gain, improved feed efficiency, and prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed. In addition, ractopamine and monensin when administered at 9.8 to 24.6 g/ton ractopamine hydrochloride and 10 to 30 g/ton monensin sodium are safe and effective for increased rate of weight gain, improved feed efficiency, increase carcass leanness, and prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

Pursuant to 21 CFR 514.106 (b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs.

The drugs are to be fed in Type C medicated feeds, in accordance with section 1 of the FOI Summary and the Blue Bird labeling that is attached to this document.

The Center for Veterinary Medicine has concluded that, for these products, adequate directions for use by the lay person have been provided. Label directions provide detailed instruction in plain language. The drug products are not controlled substances. The drug products in this feed combination are OTC when dispensed separately. Thus, the drug products are assigned OTC status, and the labeling is adequate for the intended use.

Ractopamine hydrochloride is under the following US patent numbers:

U.S. Patent Number	Date of Expiration
4,690,951	September 1, 2004
5,643,967	July 1, 2014

6. **ATTACHMENTS**:

Facsimile Labeling is attached as indicated below:

Type B Medicated Feed Blue Bird Label (OPTAFLEXX and RUMENSIN)
Type B Medicated Feed Blue Bird Label with Carcass Leanness Claim (OPTAFLEXX and RUMENSIN Plus)
Type B Liquid Medicated Feed Blue Bird Label (OPTAFLEXX and RUMENSIN)
Type B Liquid Medicated Feed Blue Bird Label with Carcass Leanness Claim (OPTAFLEXX and RUMENSIN Plus)
Type C Medicated Feed Blue Bird Label (OPTAFLEXX and RUMENSIN)

Type C Medicated Feed Blue Bird Label with Carcass Leanness Claim (OPTAFLEXX and RUMENSIN Plus)