Date of Approval: October 12, 2007

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-224

OPTAFLEXX plus RUMENSIN plus TYLAN

(Ractopamine Hydrochloride and Monensin USP and Tylosin Phosphate)
Type A Medicated Articles
For Use in the Manufacture of Type B and C Medicated Feed
Cattle Fed in Confinement for Slaughter

This supplement provides for revised dosing for the combined use of ractopamine hydrochloride, monensin USP, and tylosin phosphate for cattle fed in confinement for slaughter, based on the December 1, 2006, supplemental approval for RUMENSIN (under NADA 095-735), which provided for an increase in the upper dosage limit in cattle being fed in confinement for slaughter. This supplement also updates the name of one of tylosin's targeted bacteria to *Arcanobacterium (Actinomyces) pyogenes*, based on the November 7, 2006, supplemental approval for TYLAN (under NADA 012-491).

Sponsored by:

Elanco Animal Health

A Division of Eli Lilly and Company

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	NADA 141-224
B. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
C. Proprietary Names:	OPTAFLEXX plus RUMENSIN plus TYLAN
D. Established Names:	Ractopamine hydrochloride, monensin USP, and tylosin phosphate
E. Pharmacological Categories:	Ractopamine hydrochloride – Beta adrenergic agonist Monensin USP – Ionophore/anticoccidial Tylosin phosphate – Antibiotic
F. Dosage Forms:	Type A medicated articles to be used in the manufacture of Type B and C medicated feeds
G. Amount of Active Ingredients:	Ractopamine hydrochloride: 45.4 grams per pound (100 grams per kilogram) Monensin USP – 80 grams per pound Tylosin phosphate: 40 and 100 grams per pound
H. How Supplied:	Ractopamine hydrochloride – 25 lb bag Monensin USP – 50 lb bag Tylosin phosphate – 50 lb bag
I. How Dispensed:	OTC
J. Dosages:	Ractopamine is fed at a concentration of 8.2 to 24.6 g of ractopamine hydrochloride per ton of complete feed (based on 90% dry matter basis) to provide 70 to 430 mg ractopamine/head/day for increased rate of weight gain and improved feed efficiency in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

Ractopamine is fed at a concentration of 9.8 to 24.6 g of ractopamine hydrochloride per ton of complete feed (based on 90% dry matter basis) to provide 90 to 430 mg ractopamine/head/day 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.

Monensin is added to feedlot cattle diets at concentrations of 10 to 40 g of monensin USP per ton of complete feed at a rate of 0.14 to 0.42 mg monensin/lb of body weight, depending on severity of coccidiosis challenge, up to 480 mg monensin/head/day.

Tylosin is added to the cattle diets at concentrations of 8 to 10 g of tylosin phosphate per ton of complete feed to provide 60 to 90 mg tylosin/head/day.

K. Route of Administration: Oral, in feed

L. Species/Class: Cattle fed in confinement for slaughter

M. Indications:

Ractopamine hydrochloride (8.2 to 24.6 g/ton):
For increased rate of weight gain, improved feed efficiency, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* and reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed.

Ractopamine hydrochloride (9.8 to 24.6 g/ton):
For increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* and reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* in cattle fed in confinement for slaughter for the

last 28 to 42 days on feed.

N. Effects of Supplement: This supplement provides for revised dosing for the combined use of ractopamine hydrochloride, monensin USP, and tylosin phosphate for cattle fed in confinement for slaughter, based on the December 1, 2006, supplemental approval for RUMENSIN (under NADA 095-735), which provided for an increase in the upper dosage limit in cattle being fed in confinement for slaughter. This supplement also updates the name of one of tylosin's targeted bacteria to *Arcanobacterium (Actinomyces) pyogenes*, based on the November 7, 2006, supplemental approval for TYLAN (under NADA 012-491).

II. 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 hydrochloride 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 USP, as provided by Elanco Animal Health, has previously been separately approved (in a supplemental approval dated December 1, 2006) 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)). Tylosin phosphate as provided by Elanco Animal Health, has previously been separately approved for use in cattle fed in confinement for slaughter for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* (21 CFR 558.625(f)(1)(i)(b)). Effectiveness of each drug, ractopamine hydrochloride, monensin USP, and tylosin phosphate, 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 hydrochloride, NADA 095-735 for monensin USP, and NADA 012-491 for tylosin phosphate.

Ractopamine hydrochloride, monensin USP, and tylosin phosphate are each intended for a different use; therefore, the NADA need not demonstrate, by substantial evidence, that ractopamine hydrochloride, monensin USP or tylosin phosphate, contributes to the labeled effectiveness of the combination. Ractopamine hydrochloride, monensin USP, and tylosin phosphate 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 hydrochloride is approved for increased rate of weight gain, improved feed efficiency, and increased carcass leanness; monensin USP, for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuerni*i; and tylosin phosphate for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes*.

III. 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 hydrochloride 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 USP, as provided by Elanco Animal Health, has previously been separately approved (in a supplemental approval dated December 1, 2006) 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)). Tylosin phosphate, as provided by Elanco Animal Health, has previously been separately approved for use in cattle fed in confinement for slaughter for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* (21 CFR 558.625(f)(1)(i)(b)).

Under the provisions of ADAA, this original approval allows for the combination of ractopamine hydrochloride, monensin USP, and tylosin phosphate (as provided by Elanco Animal Health). Target animal safety of each drug, ractopamine hydrochloride, monensin USP, and tylosin phosphate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADAs 141-221, 95-735, and 12-491, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of ractopamine hydrochloride, monensin USP, and tylosin phosphate 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 141-224.

IV. HUMAN FOOD 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 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. Toxicology:

Safety of the individual drugs in this combination product has been established by data in NADA 095-735 for monensin (FOI Summary dated December 1, 2006), NADA 012-491 for tylosin phosphate (FOI Summary dated November 8, 1996) and NADA 141-221 for ractopamine hydrochloride (FOI Summary dated June 13, 2003).

B. Residue Chemistry:

1. Residue Chemistry Study:

Data demonstrating residue depletion and assay noninterference for the drugs in this combination have been summarized in the FOI Summary for the supplemental approval of NADA 141-233 dated September 11, 2007.

2. Target Tissue and Marker Residue Assignment:

The marker residue for ractopamine is parent ractopamine and the target tissue in cattle is liver (NADA 141-221, *op. cit.*). No marker residue or target tissue is specified for monensin or tylosin.

3. Tolerance Assignments:

The tolerances for ractopamine, expressed as the hydrochloride salt, are 0.09 ppm in cattle liver and 0.03 ppm in cattle muscle (21 CFR 556.570). The tolerances for monensin in cattle are 0.05 ppm in muscle, kidney and fat, and 0.10 ppm for liver (21 CFR 556.420). The tolerance for residues of tylosin is 0.2 ppm in fat, muscle, liver and kidney of cattle (21 CFR 556.740).

4. Withdrawal Period:

Monensin USP, tylosin phosphate, and ractopamine hydrochloride are approved with a zero withdrawal period. The data referred to in NADA 141-233 support the assignment of a zero withdrawal period for the subject combination.

C. Microbial Food Safety:

The Agency determined that an assessment of the microbial food safety associated with this supplement for the combination of monensin USP, tylosin phosphate, and ractopamine hydrochloride for use in cattle, previously approved pursuant to the provisions of the Animal Drug Availability Act (1996), was not necessary at this time.

D. Analytical Method for Residues:

Refer to NADA 141-221 for ractopamine hydrochloride (*op. cit.*), to NADA 012-491 for tylosin phosphate (*op. cit.*) and to NADA 095-735 for monensin USP (*op. cit.*) for the approved regulatory methods.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to OPTAFLEXX:

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.

The representative (Blue Bird) labeling for the Type B and Type C medicated feeds contains no information regarding safety to humans handling, administering, or exposed to the combination of RUMENSIN and TYLAN. This is based upon review of the Material Safety Data Sheets (MSDS) for RUMENSIN and TYLAN, as well as the MSDS sheet for OPTAFLEXX, and the individually approved Blue Bird labeling.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that OPTAFLEXX plus RUMENSIN plus TYLAN, when used according to the label, is safe and effective for increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, and reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed. Additionally, data demonstrate that residues in food products derived from cattle fed in confinement for slaughter treated with OPTAFLEXX plus RUMENSIN plus TYLAN will not represent a public health concern when the product is used according to the label.

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

A. Marketing Status:

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the lay person have been provided. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the drug product is assigned OTC status, and the labeling is adequate for the intended use.

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. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Final Printed Labeling:

Ractopamine, Monensin, and Tylosin Type B Medicated Cattle Feed
Ractopamine, Monensin, and Tylosin Plus Type B Medicated Cattle Feed
Ractopamine, Monensin, and Tylosin Liquid Type B Medicated Cattle Feed
Ractopamine, Monensin, and Tylosin Plus Liquid Type B Medicated Cattle Feed
Ractopamine, Monensin, and Tylosin Type C Medicated Cattle Feed
Ractopamine, Monensin, and Tylosin Plus Type C Medicated Cattle Feed