Date of Approval: September 11, 2007

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-233

OPTAFLEXX plus RUMENSIN plus TYLAN plus MGA

Ractopamine Hydrochloride and Monensin USP and Tylosin Phosphate and Melengestrol Acetate
Type A Medicated Articles
For Use in the Manufacture of Type C Medicated Feeds
Heifers Fed in Confinement for Slaughter

This supplement provides for revised dosing for the combined use of ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate for heifers fed in confinement for slaughter, based on the December 1, 2006, supplemental approval for RUMENSIN (under NADA 095-735). 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). In addition, this supplement increases the monensin tolerance in cattle liver from 0.05 to 0.10 ppm.

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly and Company

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-233
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 plus MGA
D. Established Names:	Ractopamine hydrochloride, monensin USP, tylosin phosphate and melengestrol acetate
E. Pharmacological Categories:	Ractopamine hydrochloride – Beta adrenergic agonist Monensin USP – Ionophore/anticoccidial Tylosin phosphate – Antibiotic Melengestrol acetate – Steroid hormone
F. Dosage Forms:	Type A medicated articles to be used in the manufacture of Type 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 Melengestrol acetate – 200 and 500 mg per pound
H. How Supplied:	Ractopamine hydrochloride – 25 lb bag Monensin USP – 50 lb bag Tylosin phosphate – 50 lb bag Melengestrol acetate – 50 lb bag (dry), 40 lb container (liquid)
I. How Dispensed:	OTC
J. Dosages:	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 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/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.

Melengestrol acetate is added to the diet of heifers at 0.5 to 2.0 pounds per head per day of medicated feed containing 0.125 to 1.0 mg melengestrol acetate per pound to provide 0.25 to 0.5 mg melengestrol acetate/head/day in heifers being fed for slaughter.

K. Routes of Administration: Oral, in feed

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

M. Indications: For increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* and suppression of estrus (heat) in heifers 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, tylosin phosphate and melengestrol acetate for heifers 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). In addition, this supplement increases the monensin tolerance in cattle liver from 0.05 to 0.10 ppm.

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)). Melengestrol acetate as provided by Pfizer, Inc., has previously been separately approved for use in cattle for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) in heifers fed in confinement for slaughter (21 CFR 558.342(e)(1)). Effectiveness of each drug, ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate 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, NADA 012-491 for tylosin phosphate, and Pfizer, Inc.'s NADAs 039-402 and 034-254 for melengestrol acetate, to which Elanco Animal Health has right of reference.

Ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate are each intended for a different use; therefore, the NADA need not demonstrate, by substantial evidence, that ractopamine hydrochloride, monensin USP, tylosin phosphate, or melengestrol acetate contributes to the labeled effectiveness of the combination. Ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate provide appropriate concurrent use because these drugs are intended to treat different conditions likely to occur simultaneously in heifers fed in confinement for slaughter during the last 28 to 42 days on feed. (Ractopamine hydrochloride, for increased carcass leanness; monensin USP, for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*; Tylosin phosphate for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes*; and melengestrol acetate for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat).)

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)). Melengestrol

acetate as provided by Pfizer, Inc., has previously been separately approved for use in cattle for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) in heifers fed in confinement for slaughter (21 CFR 558.342(e)(1)).

Under the provisions of ADAA, this original approval allows for the combination of ractopamine hydrochloride, monensin USP, tylosin phosphate (as provided by Elanco Animal Health), and melengestrol acetate (as provided by Pfizer, Inc.). Target animal safety of each drug, ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate 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, and Pfizer, Inc.'s NADAs 39-402 and 34-254 for melengestrol acetate, to which Elanco Animal Health has right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate 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 141-233.

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 USP (FOI Summary dated December 1, 2006), NADA 140-863 for ractopamine hydrochloride (FOI Summary dated December 22, 1999), NADA 012-491 for tylosin phosphate (FOI Summary dated November 8, 1996), and NADA 034-254 for melengestrol acetate (FOI Summary dated June 29, 1994).

B. Residue Chemistry:

1. Summary of Residue Chemistry Study

a. Non-clinical Laboratory Study: Residue Depletion in Beef Cattle Following Oral Administration of Monensin, Ractopamine, Tylosin and Melengestrol Acetate (heifers only) for 24 Days. HMS 041004

Study Director: Terry TerHune, DVM, PhD
HMS Veterinary Development, Inc.
Tulare, CA 93274

The purpose of this study was to evaluate the depletion of an increased dose of monensin in combination with ractopamine hydrochloride, tylosin phosphate, and melengestrol acetate (heifers only) from the liver and perirenal fat of cattle treated for 24 days. The level of monensin in this study was increased from 30 g/ton to 40 g/ton.

Twelve healthy cattle were segregated by gender (four steers and eight heifers) and were then randomly assigned to one of three treatment groups: control, monensin at 40 g/ton in combination with tylosin phosphate at 10 g/ton and ractopamine hydrochloride at 24.6 g/ton administered daily as Type C Medicated feed, melengestrol acetate administered daily as a Type B Medicated Top Dress that had been formulated to deliver a target dose of 0.5 mg/head/day. The animals were euthanized for target tissue collection on Day 24. Liver and perirenal fat tissues were collected for the residue assay.

Individual liver samples from each animal were analyzed for monensin and tylosin by microbiological methods and for ractopamine by high performance liquid chromatography with fluorescence detection. Fat tissue was collected and assayed for melengestrol acetate residue by gas chromatography with electron capture detection.

Liver samples analyzed for ractopamine and tylosin were all below the codified tolerances of 90 ppb and 0.2 ppm, respectively. Nine of ten monensin samples were less than the tolerance of 0.050 ppm; one sample contained 0.053 ppm monensin. Perirenal fat samples from the 5 heifers treated with melengestrol acetate were below the lower limit of quantitation (10 μg/kg), and, therefore, below the tolerance of 25 ppb.

Assay noninterference was previously established for this combination in the FOI Summary dated July 2, 2004, for the original approval.

2. Target Tissue and Marker Residue Assignment

The marker residue for ractopamine is parent ractopamine and the target tissue in cattle is liver (NADA 140-863, FOI Summary, *op. cit*.). No marker residue and target tissue is specified for tylosin, monensin or melengestrol acetate.

3. Tolerance Assignments

The tolerance for ractopamine, expressed as the hydrochloride salt, is 0.09 ppm in cattle liver (21 CFR 556.570). The tolerance for residues of tylosin is 0.2 ppm in fat, muscle, liver, and kidney of cattle (21 CFR 556.740). The tolerance for melengestrol acetate is 25 ppb in fat of cattle (21 CFR 556.380).

The tolerance for residues of monensin is 0.05 ppm in edible tissues of cattle (21 CFR 556.420). However, because the data in Section IV.B.1. suggest the possibility of an occasional liver sample from cattle sacrificed at practical zero withdrawal exceeding 0.05 ppm, FDA is increasing the tolerance for monensin in liver to 0.10 ppm. The total residue data already summarized in NADA 095-735 (FOI Summary dated October 28, 2004) demonstrate that when cattle were dosed with 918-1125 mg/head/day radiolabeled monensin (i.e., about 2 times the dose of 480 mg/head/day as delivered by 40 g/ton in feed) and sacrificed at practical zero withdrawal, the edible tissues contained residues that were much less than the respective safe concentrations of 1.5 ppm for muscle, 4.5 ppm for liver and 9.0 ppm for kidney and fat.

Therefore, although the dose rate of 40 g/ton or 480 mg/head/day does not present a human food safety issue, it conceivably could cause a compliance issue (with no human food safety implications) by giving an occasional positive in a monitoring program using the codified tolerance of 0.05 ppm for cattle liver. The increase of the tolerance for monensin in liver to 0.10 ppm would ensure that no violations would occur, while maintaining human food safety.

4. Withdrawal Period

Each of the four components of the combination is approved with a zero withdrawal period. With the increase in the liver tolerance for monensin, the combination qualifies for a zero withdrawal.

C. Microbial Food Safety:

The Agency determined that an assessment of the microbial food safety associated with this supplement to the combination of monensin USP, ractopamine hydrochloride, melengestrol acetate, and tylosin phosphate 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 (FOI Summary dated June 13, 2003), and to the NADAs for the other three components of the combination (*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 C medicated feeds contains no information regarding safety to humans handling, administering, or exposed to the combination of RUMENSIN, TYLAN, and MGA. This is based upon review of the MSDS sheets for RUMENSIN, TYLAN, and MGA, 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 plus MGA, 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*, reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* and suppression of estrus (heat) in heifers fed in confinement for slaughter for the last 28 to 42 days on feed. Additionally, data demonstrate that residues in food products derived from heifers fed in confinement for slaughter treated with OPTAFLEXX plus RUMENSIN plus TYLAN plus MGA 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 sections 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:

Heifer Supplement Medicated (Type C Medicated Feed) for Beef and Dairy Heifers
Liquid Heifer Supplement Medicated (Type C Medicated Feed) For Beef and Dairy Heifers
Ractopamine, Monensin, and Tylosin Plus Type C Medicated Cattle Feed