Date of Approval: August 24, 2015

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-585

ACTOGAIN 45 plus RUMENSIN plus TYLOVET 100

Ractopamine Hydrochloride plus Monensin USP plus Tylosin Phosphate

Type A Medicated Articles for Use in the Manufacture of Type B and Type C Medicated Feeds

Cattle Fed in Confinement for Slaughter

Ractopamine hydrochloride (8.2 to 24.6 g/ton) in combination with monensin USP (10 to 40 g/ton) and tylosin phosphate (8 to 10 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) in combination with monensin USP (10 to 40 g/ton) and tylosin phosphate (8 to 10 g/ton): For increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *E. 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 top dress (not to exceed 800 g/ton) plus monensin USP (10 to 40 g/ton) in combination with tylosin phosphate (8 to 10 g/ton): For increased rate of weight gain, improved feed efficiency, prevention and control of coccidiosis due to *E. bovis* and *E. zuernii* and reduction in incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium* (*Actinomyces*) *pyogenes* in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-585

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

ACTOGAIN 45 plus RUMENSIN plus TYLOVET 100

D. Product Established Name

ractopamine hydrochloride plus monensin USP plus tylosin phosphate

E. Pharmacological Category

Ractopamine hydrochloride – beta-adrenergic agonist
Monensin USP – ionophore/anticoccidial
Tylosin phosphate – antimicrobial

F. Dosage Form

Type A medicated articles for use in the manufacture of Type B (dry and liquid) and Type C medicated feeds.

G. Amount of Active Ingredient in Currently Marketed Products*

Ractopamine hydrochloride - 45.4 g/lb
Monensin USP - 90.7 g/lb
Tylosin phosphate - 100 g/lb

*****The sponsors of these individual currently marketed Type A medicated articles may have approvals for other strengths of these products 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 the Type C medicated feed that is the subject of this approval.

H. How Supplied

ACTOGAIN 45 (ractopamine hydrochloride) 25 lb (11.34 kg) bag
RUMENSIN (monensin USP) 55.12 lb (25 kg) bag; 600 kg bag
TYLOVET 100 (tylosin phosphate) 50 lb (22.68 kg) bag

I. Dispensing Status

OTC

J. Dosage Regimen

Type C Medicated Cattle Feed:

Ractopamine is fed at concentrations of 8.2 to 24.6 g ractopamine hydrochloride per ton of complete feed (based on 90% dry matter basis) to provide 70 - 430 mg ractopamine/head/day in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

Ractopamine is fed at concentrations of 9.8 to 24.6 g 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 the cattle ration at concentrations of 10 to 40 g monensin USP per ton of complete feed to provide 0.14 to 0.42 mg monensin/lb of body weight/day, depending on severity of coccidiosis challenge, up to a maximum of 480 mg monensin/head/day.

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

Ractopamine top dress feed for use with rations containing monensin and tylosin:

Feed a minimum of 1.0 lb/head/day ractopamine (not to exceed concentrations of 800 g/ton ractopamine hydrochloride) Type C top dress feed continuously to cattle fed in confinement for slaughter, to provide 70 to 400 mg/head/day ractopamine for the last 28 to 42 days on feed. Feed on top of a ration containing 10 to 40 g/ton monensin and 8 to 10 g/ton tylosin phosphate, to provide 0.14 to 0.42 mg monensin/lb body weight/day, depending on the severity of the coccidiosis challenge, up to 480 mg/head/day and 60 to 90 mg/head/day tylosin.

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) in combination with monensin USP (10 to 40 g/ton) and tylosin phosphate (8 to 10 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) in combination with monensin USP (10 to 40 g/ton) and tylosin phosphate (8 to 10 g/ton): For increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *E. 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 top dress (not to exceed 800 g/ton) plus monensin USP (10 to 40 g/ton) in combination with tylosin phosphate (8 to 10 g/ton): For increased rate of weight gain, improved feed efficiency, prevention and control of coccidiosis due to *E. bovis* and *E. zuernii* and reduction in incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium* (*Actinomyces*) *pyogenes* in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

N. Approved Original Generic Type A Medicated Articles

ACTOGAIN 45; ractopamine hydrochloride; ANADA 200-548; Zoetis Inc.
TYLOVET 100; tylosin phosphate; ANADA 200-484; Huvepharma AD

O. Reference Listed New Animal Drug

The reference listed new animal drug is a combination of OPTAFLEXX 45 plus RUMENSIN plus TYLAN; ractopamine hydrochloride plus monensin USP plus tylosin phosphate; NADA 141-224; Elanco Animal Health, A Division of Eli Lilly & Co.

The individual Type A medicated articles approved for use in the manufacture of combination medicated feeds:

OPTAFLEXX 45; ractopamine hydrochloride; NADA 141-221; Elanco Animal Health, A Division of Eli Lilly & Co.

RUMENSIN; monensin USP; NADA 095-735; Elanco Animal Health, A Division of Eli Lilly & Co.

TYLAN; tylosin phosphate; NADA 012-491; Elanco Animal Health, A Division of Eli Lilly & Co.

II. BIOEQUIVALENCE:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an ANADA may be submitted for a generic version of an approved new animal drug (reference listed new animal drug). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

According to CVM's fourth policy letter issued on November 2, 1989, with regard to the implementation of GADPTRA, after the approval of an ANADA for a generic Type A medicated article, the generic sponsor is entitled to approval for all the feed-mixed combinations for which the RLNAD is approved. Bioequivalence and tissue residue studies are not required for the approval of the generic feed use combinations (Type B or C medicated feeds). Ractopamine hydrochloride is codified under 21 CFR 558.500, monensin USP is codified under 21 CFR 558.355, and tylosin phosphate is codified under 21 CFR 558.625. The combination of ractopamine hydrochloride plus

monensin USP plus tylosin phosphate is codified under 21 CFR 558.500(e)(2)(iv), 21 CFR 558.500(e)(2)(ix) and 21 CFR 558.500(e)(2)(xiii).

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY:

The following are assigned to this product for cattle:

A. Acceptable Daily Intake and Tolerances for Residues:

The acceptable daily intake (ADI) for total residues of ractopamine hydrochloride is 1.25 micrograms per kilogram of bodyweight per day, and for monensin USP, it is 12.5 micrograms per kilogram of bodyweight per day. An ADI is not cited for total residues of tylosin phosphate. The tolerances established for the feed use RLNAD apply to the generic feed use combination new animal drug product. A tolerance of 0.09 ppm is established for ractopamine (the marker residue) in liver of cattle (the target tissue) and 0.03 ppm in muscle of cattle under 21 CFR 556.570(b)(1). A tolerance of 0.10 ppm is established for monensin in liver of cattle and and 0.05 ppm in muscle, kidney, and fat of cattle under 21 CFR 556.420(b)(1)(i) and (ii), respectively. A tolerance of 0.2 ppm (negligible residue) is established for tylosin in uncooked fat, muscle, liver, and kidney of cattle under 21 CFR 556.740(b) and a tolerance of 0.05 ppm (negligible residue) in milk under 21 CFR 556.740(d).

B. Withdrawal Periods:

Because a waiver from the requirement to demonstrate bioequivalence was granted for the Type A medicated articles, ACTOGAIN 45 and TYLOVET 100, the withdrawal periods for the combination Type B and Type C medicated feeds are those previously assigned to the RLNAD product.

When used together, ractopamine hydrochloride plus monensin USP plus tylosin phosphate are approved with a zero day withdrawal period.

C. Regulatory Method for Residues:

The determination of residues of ractopamine in the liver and muscle of cattle, swine and turkeys is by High Performance Liquid Chromatography (HPLC). The confirmation of residues of ractopamine in the liver and muscle of cattle, swine and turkeys is by Liquid Chromatography/Electrospray Ionization Triple Tandem Quadrupole Mass Spectrometry (LC/ESI-MS-MS).

The regulatory analytical method for monensin is the method developed by Eli Lilly & Co., Box 708, Greenfield, IN 46140 (Method 5801654, "Determination of Monensin in Tissues and Eggs").

The analytical method for the determination of tylosin residues in tissues uses a microbiological assay procedure. This method is found in the Food Additives Analytical Manual.

All three of the above methods are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

VI. USER SAFETY:

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ACTOGAIN 45 plus RUMENSIN plus TYLOVET 100:

The active ingredient, 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 ractopamine hydrochloride formulation (Type A medicated article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling ractopamine hydrochloride, 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 1-888-963-8471.

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that ACTOGAIN 45 plus RUMENSIN plus TYLOVET 100, when used according to the label, are safe and effective.

Additionally, data demonstrate that residues in food products derived from species treated with ACTOGAIN 45 plus RUMENSIN plus TYLOVET 100 will not represent a public health concern when the product is used according to the label.