Date of Approval: June 2, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-562

ACTOGAIN 45 plus RUMENSIN plus TYLAN plus MGA

ractopamine hydrochloride plus monensin USP plus tylosin phosphate plus melengestrol acetate

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

Heifers Fed in Confinement for Slaughter

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.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-562

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

ACTOGAIN 45 plus RUMENSIN plus TYLAN plus MGA

D. Established Name

ractopamine hydrochloride plus monensin USP plus tylosin phosphate plus melengestrol acetate

E. Pharmacological Category

Ractopamine hydrochloride – beta-adrenergic agonist
Monensin USP – ionophore/anticoccidial
Tylosin phosphate – antimicrobial
Melengestrol acetate – steroid hormone

F. Dosage Form

Type A medicated articles for use in the manufacture of Type C medicated feeds

G. Amount of Active Ingredients in Currently Marketed Products*

Ractopamine hydrochloride – 45.4 g/lb
Monensin USP – 90.7 g/lb
Tylosin phosphate – 40 and 100 g/lb
Melengestrol acetate – 200 and 500 mg/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 (ractopamine hydrochloride) 45 – 25 lb bag
RUMENSIN (monensin USP) – 25 kg bag
TYLAN (tylosin phosphate) – 50 lb bag
MGA (melengestrol acetate) – 50 lb bag (dry), 40 lb container (liquid)

I. Dispensing Status

OTC

J. Dosage Regimen

Ractopamine is fed at concentrations 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. Route 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. Approved Original Generic Type A Medicated Article

ACTOGAIN 45; ractopamine hydrochloride; ANADA 200-548; Zoetis Inc.

O. Reference Listed New Animal Drugs

The reference listed new animal drug is a combination of OPTAFLEXX (ractopamine hydrochloride) plus RUMENSIN (monensin USP) plus TYLAN (tylosin phosphate) plus MGA (melengestrol acetate) Type A medicated articles, sponsored by Elanco Animal Health, A Division of Eli Lilly & Co., under NADA 141-233.

The individual Type A medicated articles approved in this combination feed are individually approved as follows:

OPTAFLEXX; 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.

MGA; melengestrol acetate, NADA 034-254; Zoetis Inc.

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 abbreviated new animal drug application (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, tylosin phosphate is codified under 21 CFR 558.625, and melengestrol acetate is codified under 21 CFR 558.342. The combination of ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate is codified under 21 CFR 558.500(e)(2)(x).

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. Tolerances for Residues:

The tolerances established for the feed use RLNAD apply to the generic feed use combination new animal drug product.

The tolerance for ractopamine hydrochloride (the marker residue) is 0.09 parts per million (ppm) in the liver (the target tissue), and 0.03 ppm in the muscle, under 21 CFR 556.570(b)(1). The acceptable daily intake (ADI) for total residues

of ractopamine hydrochloride is 1.25 micrograms per kilogram of body weight per day.

The tolerance for monensin is 0.1 ppm in the liver, and 0.05 ppm in the muscle, kidney, and fat, under 21 CFR 556.420(b)(1). The ADI for total residues of monensin is 12.5 micrograms per kilogram of body weight per day.

The tolerance for tylosin phosphate is 0.2 ppm in uncooked fat, muscle, liver, and kidney, under 21 CFR 556.740(b), and 0.05 ppm in milk under 21 CFR 556.740(d).

The tolerance for residues of melengestrol acetate in fat is 25 parts per billion under 21 CFR 556.380.

B. Withdrawal Periods:

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

When used together, ractopamine hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate are approved with a zero-day withdrawal period.

C. Regulatory Method for Residues:

The validated regulatory methods for the determination and confirmation of residues of ractopamine hydrochloride, monensin USP, and tylosin phosphate are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

The determination of residues of ractopamine in the liver and muscle of cattle is by High Performance Liquid Chromatography (HPLC). The confirmation of residues of ractopamine in the liver and muscle of cattle 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 on file at the Center for Veterinary Medicine.

The analytical method for the determination of melengestrol acetate in tissues uses a gas chromatographic assay procedure. This method is found in Official Methods of Analysis of AOAC International, 16th edition.

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 ractopamine hydrochloride:

WARNING
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.

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 TYLAN plus MGA, when used according to the label, is safe and effective.