Date of Approval: December 12, 2009

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-301

TOPMAX plus COBAN

Ractopamine Hydrochloride and Monensin, USP
Type A Medicated Articles to be used in the Manufacture of Type C Medicated Feeds
Finishing Tom and Hen Turkeys

Ractopamine hydrochloride 4.6 to 11.8 g/ton and monensin, USP 54 to 90 g/ton: For increased rate of weight gain and improved feed efficiency in finishing tom turkeys fed continuously for the last 14 days prior to slaughter, and for the prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides, E. meleagrimitis* and *E. gallopavonis*.

Ractopamine hydrochloride 4.6 to 11.8 g/ton and monensin, USP 54 to 90 g/ton: For increased rate of weight gain and improved feed efficiency in finishing hen turkeys fed continuously for the last 7 to 14 days prior to slaughter, and for the prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides*, *E. meleagrimitis* and *E. gallopavonis*.

Sponsored by:

Elanco Animal Health

A Division of Eli Lilly & Co.

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## I. GENERAL INFORMATION:

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| **A. File Number:** | NADA 141-301 |
| **B. Sponsor:** | Elanco Animal Health<br>A Division of Eli Lilly & Co.<br>Lilly Corporate Center<br>Indianapolis, IN 46285<br><br>Drug Labeler Code: 000986 |
| **C. Proprietary Names:** | TOPMAX plus COBAN |
| **D. Established Names:** | Ractopamine hydrochloride and monensin, USP |
| **E. Pharmacological Category(ies):** | Ractopamine hydrochloride: beta agonist<br><br>Monensin, USP: ionophore |
| **F. Dosage Form:** | Type A medicated articles to be used in the manufacture of Type C medicated feeds |
| **G. Amount of Active Ingredients:** | Ractopamine hydrochloride: 9 grams ractopamine hydrochloride activity per pound in the Type A medicated article<br><br>Monensin, USP: 90 grams monensin, USP activity per pound in the Type A medicated article. |
| **H. How Supplied:** | Ractopamine hydrochloride: 25 lb bag<br><br>Monensin, USP: 50 lb bag |
| **I. How Dispensed:** | OTC |
| **J. Dosage:** | Ractopamine hydrochloride is added to feed at concentrations of 4.6 to 11.8 g/ton for increased rate of weight gain and improved feed efficiency in finishing tom turkeys fed for the last 14 days prior to slaughter.<br><br>Ractopamine hydrochloride is added to feed at concentrations of 4.6 to 11.8 g/ton for increased rate of weight gain and improved feed efficiency in finishing hen turkeys fed for the last 7 to 14 |

days prior to slaughter.

Monensin, USP is added to growing turkey feed at concentrations of 54 to 90 g/ton for the prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides*, *E. meleagrimitis* and *E. gallopavonis*.

**K. Route of Administration:** Oral, in feed

**L. Species/Class(es):** Finishing tom and hen turkeys

**M. Indication(s):** Ractopamine hydrochloride 4.6 to 11.8 g/ton and monensin, USP 54 to 90 g/ton: For increased rate of weight gain and improved feed efficiency in finishing tom turkeys fed for the last 14 days prior to slaughter, and for the prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides*, *E. meleagrimitis* and *E. gallopavonis*.

Ractopamine hydrochloride 4.6 to 11.8 g/ton and monensin, USP 54 to 90 g/ton: For increased rate of weight gain and improved feed efficiency in finishing hen turkeys fed for the last 7 to 14 days prior to slaughter, and for the prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides*, *E. meleagrimitis* and *E. gallopavonis*.

## II. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act (ADAA) of 1996, if the animal drugs or active ingredients intended for use in combination in an animal feed have already been separately approved for the particular uses and conditions for which they are intended for use in combination, the Center for Veterinary Medicine (CVM) 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 or animal drug intended only for the same use as another active ingredient or animal drug in the proposed 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 or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Ractopamine hydrochloride, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in finishing tom turkeys for increased rate of weight gain and improved feed efficiency when fed for the last 14 days prior to slaughter (21 CFR §558.500 (e)(3)(ii)) and for use in finishing hen turkeys for increased rate of weight gain and improved feed efficiency when fed for the last 7 to 14 days prior to slaughter (21 CFR §558.500 (e)(3)(i)). Monensin, USP, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in growing turkeys for the prevention of coccidiosis caused by *Eimeria adenoeides*, *E. meleagrimitis*, and *E. gallopavonis* (21 CFR §558.355 (f)(2)(i)). Effectiveness of each drug, ractopamine hydrochloride and monensin, USP when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health, A Division of Eli Lilly & Co.'s approved NADAs 141-290 and 130-736 for ractopamine hydrochloride and monensin, USP, respectively.

Because ractopamine hydrochloride and monensin, USP each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that ractopamine hydrochloride plus monensin, USP provide appropriate concurrent use for the intended target population. The use of ractopamine hydrochloride plus monensin, USP provides appropriate concurrent use because these drugs are intended to treat different conditions (ractopamine hydrochloride – increased rate of weight gain and improved feed efficiency and monensin, USP – prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides*, *E. meleagrimitis* and *E. gallopavonis*) likely to occur simultaneously with sufficient frequency in finishing turkeys. There is no

more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed.

## III. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or 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, CVM 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 CVM 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 CVM finds that the application fails to show that the combination is safe.

Ractopamine hydrochloride, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in finishing tom turkeys for increased rate of weight gain and improved feed efficiency when fed for the last 14 days prior to slaughter (21 CFR §558.500 (e)(3)(ii)) and for use in finishing hen turkeys for increased rate of weight gain and improved feed efficiency when fed for the last 7 to 14 days prior to slaughter (21 CFR §558.500 (e)(3)(i)). Monensin, USP, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for the prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides*, *E. meleagrimitis,* and *E. gallopavonis* (21 CFR §558.355 (f)(2)(i)).

Under the provisions of ADAA, this original approval allows for the combination of ractopamine hydrochloride (as provided by Elanco Animal Health, A Division of Eli Lilly & Co.) and monensin, USP (as provided by Elanco Animal Health, A Division of Eli Lilly & Co.). Target animal safety for each drug, ractopamine hydrochloride and monensin, USP when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health, A Division of Eli Lilly & Co.'s approved NADAs 141-290 and 130-736 for ractopamine hydrochloride and monensin, USP, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of ractopamine hydrochloride and monensin, USP 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. Therefore, in accordance with the FFDCA, as amended by the ADAA of 1996, no specific target animal safety studies are required for approval of this application.

## IV. HUMAN FOOD SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been

separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM 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 animal drug in the combination.

## A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. Safety of the individual drugs in this combination product has been established by data in NADA 095-735 for monensin (FR 58289-58290, Vol:40, No. 242, December 16, 1975), and NADA 140-863 (FOI Summary dated December 22, 1999) for ractopamine hydrochloride.

## B. Residue Chemistry:

### 1. Summary of Residue Chemistry Studies

#### a. Non-Interference Testing of Method B03903 in the Presence of Monensin

Study Number: T4V620802

Livers were collected from a total of 12 commercially available birds of various strains, and were homogenized and stored at -20°C prior to analysis. Three types of samples were prepared: samples fortified with 100 ppb monensin, samples fortified with 450 ppb ractopamine hydrochloride, and samples fortified with 100 ppb monensin and 450 ppb ractopamine hydrochloride. Analyses for ractopamine hydrochloride were done with the sponsor's method B03903, "Determination of Ractopamine Hydrochloride in Turkey Liver and Muscle Tissue by High Performance Liquid Chromatography."

The mean recovery obtained for the ractopamine, only, fortified samples was 399 ppm (89%; n = 10; % RSD = 1.9). The mean recovery obtained for the ractopamine + monensin samples was 407 ppb (90%; n = 10; % RSD = 1.0). The recovery data satisfactorily demonstrated assay noninterference.

### 2. Target Tissue and Marker Residue Assignment

The marker residue for ractopamine hydrochloride is ractopamine and the target tissue is liver (21 CFR 556.570). No marker residue and target tissue are specified for monensin, USP.

### 3. Tolerance Assignments

The tolerance for ractopamine in turkey liver is 0.45 ppm (21 CFR 556.570). A tolerance for residues of monensin in turkeys is not required (21 CFR 556.420).

### 4. Withdrawal Time(s)

Ractopamine hydrochloride and monensin are approved with zero-days withdrawal periods.

## C. Microbial Food Safety:

The Agency determined that an assessment of microbial food safety associated with this combination of ractopamine hydrochloride and monensin, approvable pursuant to the provisions of the Animal Drug Availability Act (1996), was not necessary at this time.

## D. Analytical Method for Residues:

### 1. Analytical Method

The approvals of NADA 095-735 for monensin (FR 58289-58290, Vol: 40, No. 242, December 16, 1975), and NADA 141-290 (FOI Summary dated November 12, 2008), for ractopamine hydrochloride contain the analytical method summaries for monensin and ractopamine hydrochloride in turkeys.

### 2. Availability of Method

Analytical methods for detection of residues of monensin and ractopamine hydrochloride in turkeys are available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

# V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type C medicated feed:

**WARNING:** The active ingredient in TOPMAX, ractopamine hydrochloride, is a beta-adreneric 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 TOPMAX 9 formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling TOPMAX, 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.

## VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data contained in the previously approved NADAs for TOPMAX plus COBAN demonstrate that, when they are used according to the label, they are safe and effective for increased rate of weight gain and improved feed efficiency in finishing tom turkeys fed continuously for the last 14 days prior to slaughter, for increased rate of weight gain and improved feed efficiency in finishing hen turkeys fed continuously for the last 7 to 14 days prior to slaughter, and for the prevention of coccidiosis in growing turkeys caused by *Eimeria adenoeides*, *E. meleagrimitis* and *E. gallopavonis.* Additionally, data demonstrate that residues in food products derived from species treated with TOPMAX plus COBAN will not represent a public health concern when the product is used according to the label.

### A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be following in practice.

### 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. Patent Information:

No patents were submitted with this application.

## VII. ATTACHMENTS:

Facsimile Labeling:

Ractopamine and Monensin Medicated Tom Turkey Feed Type C Medicated Feed

Ractopamine and Monensin Medicated Hen Turkey Feed Type C Medicated Feed