Date of Approval: October 23, 2009

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-172

PAYLEAN plus TYLAN

Ractopamine Hydrochloride and Tylosin Phosphate Type A Medicated Articles to be used in the Manufacture of Type B and C Medicated Feeds Finishing Swine Weighing Not Less Than 150 lbs

This supplement provides for revised indications for the combined use of ractopamine hydrochloride and tylosin phosphate in finishing swine, based on the November 13, 2008, supplemental approval for TYLAN (under NADA 012-491), which added an alternate dosage and feeding regimen for the porcine proliferative enteropathies (PPE, ileitis) claim. The new claim is: Ractopamine hydrochloride 4.5 to 9.0 g/ton and tylosin phosphate 40 to 100 g/ton for 2 to 6 weeks immediately after medicating with 250 mg tylosin tartrate (as TYLAN Soluble) per gallon in drinking water for 3 to 10 days: For increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter; for treatment and control of swine dysentery associated with *Brachyspira hyodysenteriae*; and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis*. This supplement also corrects the Type B and C medicated feed (Blue Bird) labeling for the control of swine dysentery and control of ileitis claim to reflect the two point dose approvals (40 or 100 g/ton) for tylosin phosphate rather than the range of 40 to 100 g/ton erroneously codified in 21 CFR 558.625(f)(1)(vi)(b) for tylosin phosphate.

Sponsored by:

Elanco Animal Health

A Division of Eli Lilly & Co.

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number: NADA 141-172

B. Sponsor: Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285
Drug Labeler Code: 000986

C. Proprietary Names: PAYLEAN plus TYLAN

D. Established Names: Ractopamine hydrochloride and tylosin phosphate

E. Pharmacological Categories: Ractopamine: Beta agonist

Tylosin phosphate: Antimicrobial

F. Dosage Form: Type A medicated articles to be used in the manufacture of Type B and C medicated feeds

G. Amount of Active Ingredients: Ractopamine hydrochloride: 9.0 or 45.4 grams ractopamine hydrochloride activity per pound in the Type A medicated article.

Tylosin phosphate: 10, 40 or 100 grams tylosin phosphate activity per pound in the Type A medicated article.

H. How Supplied: PAYLEAN 9 and 45: 25 lb bag

TYLAN 40, 100, and 100 CAL: 50 lb bag

I. How Dispensed: OTC

J. Dosage: Ractopamine hydrochloride is added to finishing feed at concentrations of 4.5 to 9 g/ton for increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter. No increased benefit has been shown when ractopamine concentrations in the diet are greater than 4.5 g/ton.

Tylosin phosphate is added to swine feed at concentrations of 40 to 100 g/ton of complete feed for 2 to 6 weeks immediately after medicating with 250 mg tylosin tartrate (as TYLAN Soluble) per gallon in drinking water for 3 to 10 days for treatment and control of porcine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis*.

Tylosin phosphate is added to swine feed at concentrations of 100 g/ton for at least 3 weeks followed by 40 g/ton until market weight for control of swine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*.

Tylosin phosphate is added to swine feed at concentrations of 100 g/ton for 21 days for control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*.

K. Route of Administration: Oral, in feed

L. Species/Classes: Finishing swine

M. Indications: Ractopamine hydrochloride 4.5 to 9.0 g/ton and tylosin phosphate 40 to 100 g/ton for 2 to 6 weeks immediately after medicating with 250 mg tylosin tartrate (as TYLAN Soluble) per gallon in drinking water for 3 to 10 days: For increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter; for treatment and control of swine dysentery associated with *Brachyspira hyodysenteriae*; and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis*.

Ractopamine hydrochloride 4.5 to 9.0 g/ton and tylosin phosphate 100 g/ton for at least 3 weeks followed by 40 g/ton until market weight: For

increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter; for control of swine dysentery associated with *Brachyspira hyodysenteriae*; and for control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*.

Ractopamine hydrochloride 4.5 to 9.0 g/ton and tylosin phosphate 100 g/ton: For increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter; and for control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*.

N. Effects of Supplement:

This supplement provides for revised indications for the combined use of ractopamine hydrochloride and tylosin phosphate in finishing swine, based on the November 13, 2008, supplemental approval for TYLAN (under NADA 012-491), which added an alternate dosage and feeding regimen for the porcine proliferative enteropathies (PPE, ileitis) claim. The new claim is: Ractopamine hydrochloride 4.5 to 9.0 g/ton and tylosin phosphate 40 to 100 g/ton for 2 to 6 weeks immediately after medicating with 250 mg tylosin tartrate (as TYLAN Soluble) per gallon in drinking water for 3 to 10 days: For increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter; for treatment and control of swine dysentery associated with *Brachyspira hyodysenteriae*; and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis*. This supplement also corrects the Type B and C medicated feed (Blue Bird) labeling for the control of swine dysentery and

control of ileitis claim to reflect the two point dose approval (40 or 100 g/ton) for tylosin phosphate rather than the range of 40 to 100 g/ton erroneously codified in 21 CFR 558.625(f)(1)(vi)(b) for tylosin phosphate.

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 feed for finishing swine for increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter (21 CFR 558.500(e)(1)(i). Tylosin phosphate (40 or 100 g/ton), as provided by Elanco Animal Health, a Division of Eli Lilly & Co., has previously been separately approved for use in feed for finishing swine for control of swine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(b)). Tylosin phosphate (40 to 100 g/ton), as provided by Elanco Animal Health, a Division of Eli Lilly & Co. has previously been separately approved for use in feed for finishing swine for the treatment and control of swine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(c)). Tylosin phosphate (100 g/ton), as provided by Elanco Animal health, has previously been separately approved for use in feed for finishing swine for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* (21 CFR 58.625(f)(1)(vi)(e)). Effectiveness of each drug, ractopamine hydrochloride and tylosin phosphate when administered alone in accordance

with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's, a Division of Eli Lilly & Co. approved NADAs 140-863 and 012-491 for ractopamine hydrochloride and tylosin phosphate, respectively.

Because ractopamine hydrochloride and tylosin phosphate 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 tylosin phosphate provide appropriate concurrent use for the intended target population. The use of ractopamine hydrochloride plus tylosin phosphate provides appropriate concurrent use because these drugs are intended to treat different conditions (ractopamine – increased rate of weight gain, improved feed efficiency, and increased carcass leanness, tylosin phosphate – (40 or 100 g/ton) control of swine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis,* and tylosin phosphate - (40 to 100 g/ton) treatment and control of swine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis*) likely to occur simultaneously with sufficient frequency in finishing swine. 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 feed for finishing swine for increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter (21 CFR 558.500(e)(1)(i). Tylosin phosphate (40 or 100 g/ton), as provided by Elanco Animal Health, a Division of Eli Lilly & Co. has previously been separately approved for use in feed for finishing swine for control of swine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(b)). Tylosin phosphate (40 to 100 g/ton), as provided by Elanco Animal Health, a Division of Eli Lilly

& Co. has previously been separately approved for use in feed for finishing swine for the treatment and control of swine dysentery associated with *Brachyspira hyodysenteriae* and for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(c)). Tylosin phosphate (100 g/ton), as provided by Elanco Animal Health, a Division of Eli Lilly & Co. has previously been separately approved for use in feed for finishing swine for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* (21 CFR 58.625(f)(1)(vi)(e)).

Under the provisions of ADAA, this supplemental approval allows for the combination of ractopamine hydrochloride (as provided by Elanco Animal Health, a Division of Eli Lilly & Co. and tylosin phosphate (as provided by Elanco Animal Health, a Division of Eli Lilly & Co. Target animal safety for each drug, ractopamine hydrochloride and tylosin phosphate when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's, a Division of Eli Lilly & Co. approved NADAs 140-863 and 012-491 for ractopamine hydrochloride and tylosin phosphate, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of ractopamine hydrochloride 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. 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 140-863 (FOI Summary dated December 22, 1999) for ractopamine hydrochloride and NADA 012-491 (26 FR 4369, May 19, 1961) for tylosin phosphate.

B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. NADA 140-863 (FOI Summary dated December 22, 1999) for ractopamine hydrochloride and NADA 012-491 (26 FR 4369, May 19, 1961) for tylosin phosphate contain a summary of the residue chemistry studies for ractopamine hydrochloride and tylosin phosphate in swine.

C. Microbial Food Safety:

The Agency determined that an assessment of microbial food safety associated with this combination of ractopamine and tylosin phosphate 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 approval of NADA 140-863 (FOI Summary dated December 22, 1999) for ractopamine hydrochloride and NADA 012-491 (26 FR 4369, May 19, 1961) for tylosin phosphate contain the analytical method summaries for ractopamine hydrochloride and tylosin phosphate in swine.

2. Availability of Method

Analytical methods for detection of residues of ractopamine and tylosin phosphate in cattle 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 B and C medicated feed:

WARNING: The active ingredient in Paylean®, 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 Paylean formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling Paylean, 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.

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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 PAYLEAN plus TYLAN demonstrate that, when they used according to the label, they are safe and effective for increased rate of weight gain, improved feed efficiency and increased carcass leanness, and for treatment and/or control of swine dysentery associated with *Brachyspira hyodysenteriae*; and for control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis.* Additionally, data demonstrate that residues in food products derived from swine treated with PAYLEAN plus TYLAN 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 followed in practice.

B. Exclusivity:

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) 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:

No patents were submitted with this application.

VII. ATTACHMENTS:

Facsimile Labeling:

Ractopamine and Tylosin Finishing Swine Feed Concentrate Type B Medicated Feed for Control of Swine Dysentery and Control of Ileitis

Ractopamine and Tylosin Finishing Swine Feed Concentrate Type B Medicated Feed for Treatment and Control of Swine Dysentery and Control of Ileitis

Ractopamine and Tylosin Finishing Swine Feed Concentrate Type B Medicated Feed for Control of Ileitis

Ractopamine and Tylosin Finishing Swine Feed Medicated Feed Type C Medicated Feed for Control of Swine Dysentery and Control of Ileitis

Ractopamine and Tylosin Finishing Swine Feed Medicated Feed Type C Medicated Feed for Treatment and Control of Swine Dysentery and Control of Ileitis

Ractopamine and Tylosin Finishing Swine Feed Medicated Feed Type C Medicated Feed for Control of Ileitis