Approval Date: October 20, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-172

PAYLEAN (Ractopamine hydrochloride) and TYLAN (Tylosin phosphate)

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

This supplement provides for the combined use of ractopamine hydrochloride and tylosin phosphate in swine in excess of 240 lb and reduces the maximum dose of ractopamine hydrochloride to 10 ppm (9 g/ton).

Sponsored By:

Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

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FREEDOM OF INFORMATION SUMMARY

PAYLEAN and TYLAN
Type A Medicated Articles to be Used in the Manufacture of Type C Medicated Feeds for Finishing Swine

1. 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. Established Names:	Ractopamine hydrochloride and tylosin phosphate
d. Proprietary Names:	PAYLEAN and TYLAN
e. Dosage Form:	Type A medicated articles to be used in the manufacture of Type C medicated feeds
f. How Supplied:	PAYLEAN – 25 lb bag TYLAN – 50 lb bag
g. How Dispensed:	OTC
h. 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.
i. Route of Administration:	Oral, in feed
j. Species/Class:	Finishing Swine
k. Recommended 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 finishing swine feed at concentrations of 100 g/ton for at least 3 weeks followed by 40 g/ton until market weight for the prevention of swine dysentery (vibrionic).

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

l. Pharmacological Category:

Ractopamine hydrochloride – Beta adrenergic agonist
Tylosin phosphate – Antibiotic

m. Indications:

<u>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</u>: 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 use in finishing swine for prevention of swine dysentery (vibrionic).

<u>Ractopamine hydrochloride 4.5 to 9.0 g/ton and tylosin phosphate 100 g/ton</u>: 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 prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*.

n. Effect of Supplement:

This supplement provides for the combined use of ractopamine hydrochloride and tylosin phosphate in swine in excess of 240 lb and

reduces the maximum dose of ractopamine hydrochloride to 10 ppm (9 g/ton).

2. 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 animals 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 or animal drug intended only for the same use as another active ingredient or animal drug in the 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 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, has previously been separately approved for use in 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 as provided by Elanco Animal Health, has previously been separately approved for use in finishing swine for prevention of swine dysentery (vibrionic) (21 CFR 558.625(f)(1)(vi)(b)) and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(e)). Effectiveness for each drug, ractopamine hydrochloride and tylosin phosphate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 140-863 and 012-491, 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 because these drugs are intended to treat different conditions (ractopamine hydrochloride, weight gain, feed efficiency, and carcass leanness; tylosin phosphate, swine dysentery (vibrionic) and ileitis associated with *Lawsonia intracellularis*) likely to occur simultaneously with sufficient frequency in finishing swine. There is no more than one nontopical antibacterial (tylosin phosphate) contained in this animal drug intended for use in Type C medicated feed. Ractopamine hydrochloride is not considered to be an antibacterial animal drug for such use in swine for the purpose of section 512(d)(4) of the FDDCA.

3. 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 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 as provided by Elanco Animal Health, has previously been separately approved for use in finishing swine for prevention of swine dysentery (vibrionic) (21 CFR 558.625(f)(1)(vi)(b)) and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(e)). 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 approved NADAs 140-863 and 012-491, respectively. The Agency has found no substantial scientific issues relating to the target animal safety of ractopamine hydrochloride or tylosin phosphate when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of this NADA for this combination. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety is required for approval of NADA 141-172.

4. HUMAN 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 the 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 the 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 140-863 for ractopamine hydrochloride (FOI Summary dated December 22, 1999) and NADA 012-491 for tylosin phosphate (FOI Summary dated November 8, 1996).

B. Residue Chemistry:

1. Residue Chemistry Study:

Data demonstrating residue depletion and assay noninterference for the drugs of this combination have been summarized in the FOI Summary for the original approval of this NADA dated February 20, 2001.

2. Target Tissue and Marker Residue Assignment:

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

3. Tolerance Assignments:

The tolerance for ractopamine, expressed as the hydrochloride salt, is 0.15 ppm in swine liver. The tolerance for microbiologically active residues of tylosin is 0.2 ppm in fat, muscle, liver and kidney of swine (see FOI Summaries for NADA 140-863 and 012-491, *op. cit.*).

4. Withdrawal Period:

Ractopamine hydrochloride and tylosin phosphate each are approved with a zero withdrawal period. Tissue residue non-interference was adequately shown; therefore the combination qualifies for a zero withdrawal (FOI Summary for the original approval of this NADA, *op. cit.*).

C. Microbial Food Safety:

The Agency determined that an assessment of the microbial food safety associated with this supplement to the combination of ractopamine and tylosin in Type C Medicated feeds for swine, previously approved pursuant to the provisions of the Animal Drug Availability Act (1996), was not necessary at this time.

D. Analytical Method:

Refer to the approved NADAs for ractopamine hydrochloride and tylosin phosphate for the approved regulatory methods in NADA 140-863 and 012-491, respectively (*op. cit.*).

E. User Safety Concerns:

Refer to Material Safety Data Sheets (MSDS) for these NADAs for ractopamine hydrochloride and tylosin phosphate (NADA 140-863 and 012-491 respectively) by contacting the manufacturer for the MSDS.

5. 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 of the implementing regulations. The data demonstrate that ractopamine hydrochloride (4.5 to 9.0 g/ton) and tylosin phosphate (40 to 100 g/ton) are safe and effective for the claims indicated in section 1 of this FOI Summary.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

Pursuant to 21 CFR 514.106 (b)(2), this supplemental NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs.

The drugs are to be fed in Type C medicated feeds in accordance with section 1 of the FOI Summary and the Blue Bird labeling that is attached to this document.

The Center for Veterinary Medicine has concluded that, for these products, adequate directions for use by the layperson have been provided and the products will have over-the-counter (OTC) status. Label directions provide detailed instruction in plain language. The drug products are not controlled substances. Thus, the drug products are assigned OTC status, and the labeling is adequate for the intended use.

Ractopamine hydrochloride is under the following US patent number:

U.S. Patent Number	Date of Expiration
4,690,951	September 1, 2007

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Ractopamine and Tylosin Finishing Swine Type C Medicated Feed (Blue Bird) (Rate of Weight Gain/Feed Efficiency/Carcass Leanness/Ileitis)

Ractopamine and Tylosin Finishing Swine Type C Medicated Feed (Blue Bird) (Rate of Weight Gain/Feed Efficiency/Carcass Leanness /Swine Dysentery) (Tylosin 40 g/ton)

Ractopamine and Tylosin Finishing Swine Type C Medicated Feed (Blue Bird) (Rate of Weight Gain/Feed Efficiency/Carcass Leanness /Swine Dysentery) (Tylosin 100 g/ton)