Date of Approval: November 7, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 012-491

TYLAN 40, TYLAN 100, AND TYLAN 100 CAL

Tylosin phosphate
Type A medicated article
Beef cattle, Chickens, Broiler chickens, Laying chickens,
Replacement chickens, and Swine

To add an alternative feeding regimen for the control of porcine proliferative enteropathies (PPE, ileitis) in swine: "feed 100 g tylosin per ton of complete feed for at least 3 weeks. Follow with 40 g tylosin per ton of complete feed until pigs reach market weight."

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly & Co.

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I. GENERAL INFORMATION:

A. File Number: NADA 012-491

B. Sponsor:

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

Drug Labeler Code: 000986

C. Proprietary Names: TYLAN 40, TYLAN 100, and TYLAN 100 Cal

D. Established Name: Tylosin phosphate

E. Pharmacological Category: Antimicrobial

F. Dosage Forms: Type A medicated article

G. Amount of Active Ingredient: 40 g/lb or 100 g/lb

H. How Supplied: Type C medicated feed

I. How Dispensed: OTC

J. Dosages:

Beef cattle:
8 to 10 g/ton (60 to 90 mg/head/day): Feed continuously as the sole ration.

Chickens:
4 to 50 g/ton.

Broiler chickens:
800 to 1,000 g/ton: Administer in feed to chickens 0 to 5 days of age, follow with second administration in feed for 24 to 48 hours at 3 to 5 weeks of age.

Laying chickens:
20 to 50 g/ton.

Replacement chickens:
1,000 g/ton: Administer in feed to chickens 0 to 5 days of age, follow with second administration in feed for 24 to 48 hours at 3 to 5 weeks of age.

Swine:

10 to 100 g/ton: Continuous use as follows: 20 to 100 g/ton, prestarter or starter; 20 to 40 g/ton, grower; 10 to 20 g/ton, finisher.

40 to 100 g/ton: Use 100 g/ton for at least 3 weeks followed by 40 g/ton until market weight.

40 to 100 g/ton: Administer in feed after treatment with tylosin in drinking water as tylosin base; 0.25 g/gallon in drinking water for 3 to 10 days, 40 to 100 g/ton in feed for 2 to 6 weeks.

100 g/ton.

100 g/ton: Administer for 21 days.

K. Route of Administration: Oral, in feed

L. Species/Classes: Beef cattle, Chickens, Broiler chickens, Laying chickens, Replacement chickens, and Swine

M. Indications:

Beef cattle:

For reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes.*

Chickens:

For increased rate of weight gain and improved feed efficiency.

Laying chickens:

For improved feed efficiency.

Broilers and replacement chickens:

To aid in the control of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum.*

Swine:

For increased rate of weight gain and improved feed efficiency.

For control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*.

For control of swine dysentery associated with

Brachyspira hyodysenteriae.

For maintaining weight gains and feed efficiency in the presence of atrophic rhinitis.

For treatment and control of swine dysentery associated with *Brachyspira hyodysenteriae* following initial medication with TYLAN Soluble (tylosin) in drinking water.

N. Effect of Supplement: This supplement adds an alternative feeding regimen for the control of porcine proliferative enteropathies (PPE, ileitis) in swine: "feed 100 g tylosin per ton of complete feed for at least 3 weeks. Follow with 40 g tylosin per ton of complete feed until pigs reach market weight."

II. EFFECTIVENESS:

A. Dosage Characterization:

The Freedom of Information (FOI) Summary for the supplemental approval of NADA 012-491 dated November 8, 1996, contains dosage characterization information for the control of porcine proliferative enteropathies in swine. This supplemental approval modifies the previously approved dosage regimen for the control of porcine proliferative enteropathies in swine. Additionally, the regimen is identical to a previously approved regimen for swine dysentery. Swine dysentery and porcine proliferative enteropathies are difficult to distinguish based on clinical signs alone. Therefore, 100 g tylosin/ton for three weeks followed by 40 g tylosin/ton was selected to be tested for the control of porcine proliferative enteropathies in swine.

B. Substantial Evidence:

1. Type of Study: Clinical Challenge Model Study

a. Title: "An Efficacy Dose Confirmation Study with TYLAN Premix for the Control of Porcine Proliferative Enteropathy (ileitis) in Swine." Study #T1XAM0404. August to November, 2005.

b. Investigators and Locations:
Terry TerHune, D.V.M., Ph.D., Tulare, CA (Site 1);
Nathan Winkelman, D.V.M., Rice, MN (Site 2);
Lyle Kesl, D.V.M., Ph.D., Williams, IA (Site 3)

c. Study Design:

1) *Objective*: To confirm the clinical effectiveness of tylosin phosphate, administered in a Type C medicated feed, for the control of porcine proliferative enteropathy (PPE, ileitis) in swine during an induced outbreak of ileitis, using a mucosal homogenate challenge model. This study was conducted in accordance with CVM Guidance for Industry 85, "Good Clinical Practice" (VICH GL9) May 9, 2001.

2) *Study Animals*: A total of 672, healthy, three week old female and castrated male commercial cross-breed pigs were enrolled in the study. They were obtained from separate swine sources for each study site. The animals weighed from 5.5 to 16.0 kg at enrollment, and were demonstrated to be free of *Lawsonia intracellularis* by random polymerase chain reaction (PCR) testing of fecal samples in the group prior to purchase. Pigs were not vaccinated with *L. intracellularis* vaccine.

3) *Experimental Design*: On Day 0, each pig was administered between 4.8 x 10^8 and 2.04 X 10^9 *L. intracellularis* organisms by gastric gavage. The

gavage material consisted of a mucosal homogenate prepared from sections of affected pig intestine which were obtained from a recent, North American case of PPE.

4) *Treatment Groups*: On Day -7, animals were ranked by descending weight within gender and randomly assigned to pens. Pens were then randomly assigned to treatment group (Table 1).

Table 1. Treatment Groups

Treatment Group	Dose / Regimen	Total Pens	Animals per Pen	Total Enrolled Animals
Tylosin phosphate	(Phase 1) 100 g/ton for 21 days; (Phase 2) 40 g/ton for 21 days	56	6 (3 M, 3 F)	336
Control	(Phase 1) 0 g/ton; (Phase 2) 0 g/ton	56	6 (3 M, 3 F)	336

5) *Test Article Administration*: Tylosin phosphate was administered to pigs as a Type C medicated feed containing 100 grams tylosin per ton of feed (Phase 1) followed by 40 grams tylosin per ton of feed (Phase 2). Phase 1 feed was initiated on "Day X" at each study site. "Day X" was defined as the day when at least 15% of the total population of study pigs at the study site was observed to be clinically affected with PPE in a single day. A pig was considered clinically affected when it had a diarrhea score of 2 or 3 in one observation period (see score definitions below). Phase 2 feed was initiated on Day X+21. Control group pigs received non-medicated feed throughout the study. Feed was provided to both groups on an *ad libitum* basis.

On Day X, four clinically affected pigs at each site were selected for necropsy and areas of affected intestine were tested for *L. intracellularis* by immunohistochemical (IHC) stain to confirm the presence of PPE in study animals. Not more than one pig was removed from an individual pen for this test.

6) *Measurements and Observations*: The primary variables for determining effectiveness were clinical scores (fecal color, diarrhea, abdominal gut fill, pig attitude), percent mortality, lesion index, and average daily gain (adjusted for mortality).

Clinical scores were evaluated daily from Days X+1 to X+42 according to the following criteria:

Fecal Color:
1 = Normal – no evidence of abnormal color.
2 = Darker or blood-tinged
3 = Frank blood or tarry feces

Diarrhea:
1 = Normal, no diarrhea – Feces are formed with no evidence of abnormal consistency.
2 = Semi-loose – Feces are soft: examples include "oatmeal" or "cow-pie" consistency. Fecal material will "pile or puddle" on the pen floor.
3 = Watery diarrhea – Feces are watery, containing primarily fluid *versus* solid material, readily running off the slatted floor.

Abdominal Gut Fill:
1 = Normal – No appreciable loss of body condition, flank full and rounded.
2 = Moderately gaunt – Loss of body condition, flank is flat.
3 = Severely Gaunt – Emaciated, flank very hollow.

Pig Attitude:
1 = Normal – Animal is bright, alert, and active, responding to stimuli.
2 = Slight to moderately depressed or listless – Animal slowly responds to stimuli, but may keep head/ears lowered.
3 = Severely depressed or recumbent – Animal may slowly respond to stimuli briefly, but prefers to lie back down quickly. Remains isolated from group.

The percent abnormal pig days for each clinical score was calculated for each pen by summing the total days with an abnormal score (score of 2 or 3) for all pigs in a pen and dividing this numerator by the sum of all study days for which each pig was alive, across all pigs in each pen.

Pigs that died or were euthanized from Day X+1 to Day X+42 were considered "mortalities associated with PPE" if they had intestinal lesions consistent with PPE at necropsy.

On Day X+42, all remaining pigs were euthanized, necropsied, and scored for PPE lesions according to the following criteria:

Lesion Scores:
1 = Normal; no gross lesions.
2 = Mild mesoserosal edema and hyperemia; a suspect mild PPE lesion.
3 = Edema, hyperemia, reticulated serosa and thickened mucosa; a moderate PPE lesion.
4 = Edema, hyperemia, reticulated serosa and mucosa, very gross thickening of the mucosa, blood or fibrin; a severe PPE lesion and/or necrotic enteritis.

Lesion index was calculated as the sum of the lesion score multiplied by the associated lesion length:

$$\text{Lesion Index} = \Sigma\ (i \times l_i),$$
where i = 2, 3, 4 (lesion score)
and l_i = length (cm) associated with lesion score i.

Individual pig weights and feed weights by pen were collected Days -7, 0, X, X+21, and X+42.

The data were required to meet one of the following sets of criteria in order to demonstrate effectiveness:

- At least two of the four clinical variables were statistically significantly improved ($p \leq 0.05$) in the treated group compared to the control group, **AND** mortality was not statistically higher ($p \leq 0.05$) in the treated group compared to the control group;

  OR

- Lesion index was significantly improved ($p \leq 0.05$) in the treated group compared to the control group, **AND** average daily gain was numerically improved in the treated group compared to the control group, **AND** mortality was not statistically higher ($p \leq 0.05$) in the treated group compared to the control group.

Pigs were also observed once daily from receipt to Day X+42 for general health observations including observations for survival, general condition, and adverse events.

7) *Statistical Analysis*: For each of the clinical variables (fecal color score, diarrhea score, abdominal gut fill score, pig attitude score), the percent of pig-days with abnormal scores (Score = 2 or Score = 3, as defined previously) for each pen was calculated and the arcsine transformation of pen proportions ($p' = \arcsin\sqrt{\%Abnormal}$) was used in the analysis. A general linear mixed model was used to analyze the data where number of pigs per pen at medication initiation was used as a weighting factor. The full statistical model included treatment (Tylosin, Control) as a fixed effect and site, block within site, and the site by treatment interaction as random effects. If the site by treatment interaction was not significant ($p > 0.25$) according to Wald's Test, the site by treatment interaction term was removed from the statistical model. A one-sided comparison ($\alpha = 0.05$) of tylosin versus negative control was conducted between means pooled over all sites. If the site by treatment interaction was significant ($p \leq 0.25$), treatments were compared separately at each site. The statistical model for the analysis by site included treatment as a fixed effect and block as a random effect. If the interaction was significant, at least two of the three sites should show significant improvement ($p < 0.05$) for tylosin compared to the negative control, and the third site should not show significance in an unfavorable direction.

Percent mortality was compared between the two groups pooled across all sites with the two-sided Fisher's Exact Test ($\alpha = 0.05$).

Because pig lesion index data were skewed, lesion index was transformed using a natural logarithmic transformation [LOG(1 + Lesion Index)] in order to both normalize the data and equalize treatment variances. The average pen transformed lesion index was analyzed as described for the clinical variables.

Average daily gain (ADG) was calculated for each pen. ADG was analyzed as described for the clinical variables.

d. Results: A total of 634 pigs completed the study.

1) *Clinical Scores*: Percent abnormal pig days for pig attitude and abdominal gut fill scores were pooled across study sites because no significant treatment by site interaction was evident. Both mean pig attitude score and mean abdominal gut fill score were significantly improved in the tylosin-treated group compared to the control group (Table 2).

Table 2. Pig Attitude and Abdominal Gut Fill Scores (Combined Sites)†

Treatment Group	Pig Attitude‡ (%)	Abdominal Gut Fill‡ (%)
Tylosin phosphate	0.7[a]	5.8[a]
Control	2.2[b]	14.5[b]

† Percent abnormal pig days.
‡ Values with different superscripts (a or b) within each column are statistically significantly different ($P \leq 0.05$). Values are back-transformed from least squares means (LSMeans).

Percent abnormal pig days for diarrhea and fecal color scores were evaluated by site because a significant treatment by site interaction was demonstrated for these variables. Mean diarrhea scores were significantly improved in the tylosin treated-group compared to the control group at all three sites (Table 3). Mean fecal color scores were significantly improved in the tylosin-treated group compared to the control group at Site 1 only.

Table 3. Diarrhea and Fecal Color Scores (By Site) †

Treatment Group	Diarrhea‡ (%)			Fecal Color‡ (%)		
	Site 1	Site 2	Site 3	Site 1	Site 2	Site 3
Tylosin phosphate	32.9[a]	9.8[a]	26.1[a]	0.1[a]	0.0[a]	0.1[a]
Control	58.9[b]	18.8[b]	42.9[b]	1.6[b]	0.1[a]	0.2[a]

† Percent abnormal pig days.
‡ Values with different superscripts (a or b) within each column are statistically significantly different ($P \leq 0.05$). Values are back-transformed from LSMeans.

2) *Mortality*: Percent mortality was pooled across study sites. Mortality was not statistically different ($P > 0.05$) between tylosin-treated pens and control pens. Tylosin-treated pens demonstrated numerically lower mortality (1.9%) across sites compared to control pens (3.4%).

3) *Lesion Index*: The pen mean lesion index was evaluated by site because a significant treatment by site interaction was demonstrated for this variable. The tylosin-treated group was significantly improved compared to the control group at Site 1 only (Table 4).

Table 4. Lesion Index (By Site)

Treatment Group	Lesion Index†		
	Site 1	Site 2	Site 3
Tylosin phosphate	7.0[a]	3.7[a]	2.1[a]
Control	22.8[b]	5.5[a]	2.6[a]

† Values with different superscripts (a or b) within each column are statistically significantly different ($P \leq 0.05$). Values are back-transformed from LSMeans.

4) *Average Daily Gain (ADG)*: The pen mean ADG was pooled across study sites because no significant treatment by site interaction was evident. Pen mean ADG was statistically significantly ($P \leq 0.05$) improved in the tylosin-treated group (0.60 kg/day) compared to the control group (0.54 kg/day).

5) *Secondary Variables*: Mean average daily feed intake (ADFI), mean feed to gain ratio (F/G), and mean pen total weight gain were pooled across study sites because no significant treatment by site interaction was evident. All three secondary variables were significantly improved in the tylosin treated group compared to the control group (Table 5).

Table 5. Secondary Variables (Combined Sites)†

Treatment Group	Average Daily Feed Intake (kg/day)	Feed/Gain	Pen Total Weight Gain (kg)
Tylosin phosphate	1.08[a]	1.78[a]	148[a]
Control	1.00[b]	1.82[b]	134[b]

† Values with different superscripts (a or b) within each column are statistically significantly different ($P \leq 0.05$). Values are LSMeans.

e. Adverse Reactions: No adverse reactions attributable to the test article were reported in this study.

f. Conclusion: This study demonstrates that tylosin phosphate is effective for the control of PPE when fed to swine at 100 g/ton for at least 21 days followed by 40 g/ton for at least 21 days.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The original approval of NADA 012-491 as published in the FEDERAL REGISTER [26 FR 4369] on May 19, 1961, contains summaries of target animal safety studies for swine.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The original approval of NADA 012-491 as published in the FEDERAL REGISTER [26 FR 4369] on May 19, 1961, contains summaries of all toxicology studies.

B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The original approval of NADA 012-491 as published in the FEDERAL REGISTER [26 FR 4369] on May 19, 1961, contains a summary of residue chemistry studies for swine.

C. Microbial Food Safety:

The impact of the proposed change in the feeding regimen for tylosin phosphate in swine for control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* from "feed 100 g of tylosin per ton of complete feed as the sole ration for 21 days" to "feed 100 g of tylosin per ton of complete feed as the sole ration for 21 days. Alternatively, feed 100 g of tylosin per ton of complete feed for at least three weeks. Follow with 40 g tylosin per ton of complete feed until pigs reach market weight" was carefully considered by the Agency. The Agency determined that this change should not significantly impact public health; therefore, an evaluation of microbial food safety was not necessary at this time.

D. Analytical Method for Residues:

The original approval of NADA 012-491 as published in the FEDERAL REGISTER [26 FR 4369] on May 19, 1961, contains the analytical method summaries for tylosin in swine.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to TYLAN 40, TYLAN 100, or TYLAN 100 Cal:

> Warning: TYLAN may be irritating to unprotected skin and eyes. When mixing and handling TYLAN use protective clothing and impervious gloves. In the case of accidental eye exposure, flush eyes with plenty of water. Exposed skin should be washed with plenty of soap and water. Remove and wash contaminated clothing. Seek medical attention if irritation becomes severe or persists. The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

The MSDS for tylosin was examined and the product label information is adequate.

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 demonstrate that TYLAN 40, TYLAN 100, and TYLAN 100 Cal, when used according to the label, is safe and effective for the control of porcine proliferative enteropathies associated with *Lawsonia intracellularis.* Additionally, data demonstrate that residues in food products derived from swine treated with TYLAN 40, TYLAN 100, and TYLAN 100 Cal 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:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the additional regimen for the control of porcine proliferative enteropathies (ileitis) for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA is a Category II change (21 CFR §514.106(b)(2)) to dose and treatment regimen which did not require a reevaluation of the safety or effectiveness data in the original NADA.

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

TYLAN 40 Type A medicated article
TYLAN 100 Type A medicated article
TYLAN 100 Cal Type A medicated article
BLUE BIRD Tylosin Ileitis Control Type B Medicated Swine Feed
BLUE BIRD Tylosin Swine Dysentery Control Type B Medicated Feed
BLUE BIRD Tylosin Swine Dysentery Treatment and Control Type B Medicated Feed
BLUE BIRD Tylosin Type B Medicated Cattle Feed
BLUE BIRD Tylosin Liquid Type B Medicated Cattle Feed
BLUE BIRD Tylosin Swine Ileitis Control Type C Medicated Feed
BLUE BIRD Tylosin Swine Dysentery Control Type C Medicated Feed
BLUE BIRD Tylosin Swine Dysentery Treatment and Control Type C Medicated Feed
BLUE BIRD Tylosin Type C Medicated Cattle Feed
BLUE BIRD Tylosin Type C Medicated Broiler Chicken Feed
BLUE BIRD Tylosin Type C Medicated Chicken Feed
BLUE BIRD Tylosin Type C Medicated Laying Chicken Feed
BLUE BIRD Tylosin Type C Medicated Replacement Chicken Feed