Approval Date: November 8, 1996

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 012-491

B. Sponsor

Elanco Animal Health, a Division of Eli Lily and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

C. Proprietary Name

TYLAN® 40 Type A medicated article
TYLAN® 100 Type A medicated article
TYLAN® 100 Cal Type A medicated article

D. Established Name

tylosin phosphate

E. Dosage Form

TYLAN® is available in 50-pound bags as a Type A medicated article.

F. Dispensing Status

OTC

G. Dosage Regimen

For the prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*: 100 g/ton for 21 days

H. Route of Administration

TYLAN® should be administered orally, via feed.

I. Species/Class

Swine

J. Indication

SWINE:

For the prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*;

For increased rate of weight gain and improved feed efficiency;

For prevention of swine dysentery (vibrionic);

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

For the treatment and control of swine dysentery (vibrionic) following initial medication of TYLAN® in drinking water.

II. EFFECTIVENESS

A. Dose Determination Study

Trial Number TlX399301, a single location, blinded, clinical dose study.

1. Investigator

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2. General Design

   a) Purpose: This study evaluated the efficacy of two different levels (40 g/ton and 100 g/ton) of tylosin phosphate in feed versus nonmedicated controls in a natural outbreak of porcine proliferative enteropathy (PPE) associated with *Lawsonia intracellularis* (LI). Pigs were followed to market to determine the incidence of ileal lesions at slaughter and to compare average daily gain.

   b) Experimental Animals and Diagnosis: Pigs averaging 43 lb originating from a commercial terminal cross source were placed in a facility with a clinical history of proliferative enteropathy. Approximately 30 days post-arrival, pigs exhibited poor growth rate and diarrhea. A clinically ill pig was necropsied and found to have gross and histopathological lesions consistent with PPE. Bacterial cultures for *Serpulina* spp. taken from the small and large intestine were negative. Fecal samples obtained from several pens of pigs were shown to be positive for the intracellular organism by dot blot hybridization techniques and polymerase chain reaction (PCR) methodology. Diagnosis of PPE was based upon the presence of clinical signs, gross necropsy lesions consistent with PPE, and microscopic identification of the organism using the Warthin-Starry staining technique.

   c) Randomization and Controls: One hundred and twelve (112) pigs were ranked according to clinical impression scores. Pigs within the same clinical impression category (0, 1, 2, 3) were then randomly assigned to one of eight pens. However, animal weight, previous treatment, and sex were considered before pigs were randomly assigned to pens. Two treatments, 100 g/ton and 0g/ton tylosin were then randomly assigned to the eight pens. The four pens of non-medicated pigs served as the controls. Forty-two (42) clinically normal pigs that were exposed to PPE were randomly assigned to one of three pens. Animal weight, previous treatment, and sex were considered before pigs were randomly assigned to pens. All three pens were given feed medicated with tylosin at 40 g/ton.

   d) Test Article Administration: The currently-marketed TYLAN® Type A medicated article was mixed in complete feed so that the final mixture

contained either 100grams of tylosin per ton of feed or 40 grams of tylosin per ton of feed. Pigs in the 100/40 group received tylosin at 100 g/ton for the first 21 days and 40g/ton the second 21 days. Pigs in the 40/40 group received tylosin at 40 g/ton for the first 21 days and 40 g/ton the second 21 days. Pigs in the 0/0 group received unmedicated feed for entire test period of 42 days.

e) Pertinent Variables Measured: Clinical impression scores (CIS), Average Daily Gain (ADG), Average Feed Intake (AFI), Feed/Gain (F/G), and Gain/Feed G/F) were the decision variables.

f) Results

a. Clinical Impression Scores: Clinical impression scores were collected on all animals every other day for the first 21 days. Scoring was conducted using a scale of 0 to 3, with 0 = normal, 1 = mild clinical signs (i.e., depression and gauntness), 2 = moderate clinical signs, and 3 = severe clinical signs. A comparison of pig scoring trends across days for pigs medicated at 100g/ton versus nonmedicated pigs shows the distribution of pigs in each category as very nearly the same at the beginning of the trial. As the trial progressed, the pigs receiving tylosin at 100 g/ton began returning to normalcy in a greater number and within an earlier time frame than the 40 g/ton or nonmedicated pigs. Most unmedicated pigs were not back to normal by 21 days, whereas most of the pigs treated with 100 g/ton tylosin returned to normal by Day 11. Table 4.1 summarizes clinical impression scores (CIS) for pigs on the trial during the first 21-day medication period.

Table 4.1. Daily frequency of clinical impression score (*CIS) category by treatment level (40 and 100 g/ton tylosin versus 0 g/ton) during the first 21 days of the trial.

Dosage Tylosin	0 g/ton				40 g/ton				100 g/ton			
*CIS	0	1	2	3	0	1	2	3	0	1	2	3
Trial Day												
1	4	28	18	6	41	1	0	0	4	27	20	5
3	12	14	20	10	24	14	4	0	12	15	18	11
5	5	14	23	14	17	15	10	0	13	20	14	8
7	6	7	25	18	13	17	12	0	18	16	16	6
9	7	8	21	20	9	20	13	0	25	19	10	2
11	8	15	16	17	17	20	5	0	40	10	6	0
13	5	17	22	12	24	12	5	1	36	11	8	0
15	19	19	9	9	28	11	3	0	45	7	4	0
17	20	20	11	4	27	11	4	0	41	11	4	0
19	18	17	14	5	30	7	4	0	43	8	4	1
21	17	18	13	6	32	9	1	0	49	5	2	0

* 0 = normal, 1 = mild clinical signs (i.e., depression and gauntness), 2 = moderate clinical signs, and 3 = severe clinical signs

b. Gain Variables: Average Daily Gain for pigs receiving 100g/ton tylosin in the first 21 days improved compared to pigs receiving 40g/ton and controls. The pigs receiving 40g/ton tylosin showed no improvement in average daily gain when compared to controls. No difference in average daily feed was detected when comparing the three tylosin levels (100, 40, and 0 g/ton). Feed to Gain for pigs receiving 100 g/ton tylosin in the first 21 days improved compared to pigs receiving 40 g/ton tylosin and the controls. Similarly, Feed to Gain and Gain to Feed ratios for pigs receiving 40g/ton tylosin did not improve when compared to controls. Results for weight gain and feed efficiency are presented in Table 4.2.

Table 4.2. Least squares (LS) means for Average Daily Gain (ADG), Average Daily Feed (ADF), Feed to Gain (F/G), and Gain to Feed (G/F) calculated from data in which pigs received varying levels of tylosin in the feed over 42 days.

Tylosin*	Treatment Days 0-21				Treatment Days 21-42				Treatment Days 0-42			
Dose	ADG5%	ADF	F/G&	G/F+	ADG	ADF	F/G	G/F	ADG	ADF	F/G	G/F
100/40@	1.45c	3.28	2.21a	0.45c	1.50	3.59	2.38	0.42	1.48b	3.28	2.29c	0.43c
40/40#	0.99b	3.50	3.36b	0.27b	1.07	2.77	2.63	0.49	1.03a	3.50	2.98b	0.33b
0/0$	1.27b	3.12	4.48c	0.41a	1.34	3.26	2.63	0.39	1.31	1.31a	2.45a	0.41a

* 100/40 pigs received tylosin at 100 g/ton for the first 21 days and 40 g/ton the second 21 days. Other treatments defined similarly.
@ 56 pigs in 4 pens; mean start weight 81.20 lb, mean end weight (42 days) 138.64 lb.
# 42 pigs in 3 pens; mean start weight 93.39 lb, mean end weight (42 days) 147.43 lb.
$ 56 pigs in 4 pens; mean start weight 82.47 lb, mean end weight (42 days) 133.94 lb.
% 100/40 different from 0/0 (P = 0.090), 100/40 different 40/40 (P = 0.11).
& 100/40 different from 0/0 (P = 0.07).
+ Means with different superscripts are different (P<0.05).
~ 100/40 different from 0/0 (P = 0.08), 100/40 different from 40/40 (P = 0.09).
! 100/40 different from 0/0 (P = 0.09).
^ 100/40 different from 0/0 (P = 0.08).

g) Statistical Analyses: Average Daily Gain, Average Daily Feed, Feed to Gain, and Gain to Feed ratios for pigs receiving 100, 40, or 0 g/ton tylosin were analyzed using a mixed-model analysis in which TREATMENT and INITIAL WEIGHT were fixed effects and PEN (treatment) was a random effect The results of the analysis are provided in Table 4.2. The significance of p-values reported by the firm represent alpha levels for a two-sided hypothesis test. Clinical impression scores were not analyzed statistically.
h) Conclusions: Feeding pigs 100 g/ton tylosin for 21 days was successful in controlling/preventing porcine proliferative enteropathies (PPE). However, feeding pigs 40 g/ton tylosin was marginally effective to non-effective in controlling/preventing a natural outbreak of PPE.
i) Adverse Reactions: No adverse reactions were reported by the investigative team during or upon completion of this study.

B. Field Trials

1. Investigators

T1X019503 and T1X019508
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T1X319505 and T1X319506
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2. General Design

a) Purpose: The purpose of these trials was to confirm the efficacy of tylosin phosphate, when fed to pigs at 100 g/ton for 21 days, for the prevention and/or control of PPE associated with *L. intracellularis.*

b) Experimental animals, controls, and diagnosis: The trials were conducted in commercial swine facilities in which PPE is an endemic problem. At each trial, tylosin phosphate was fed to pigs at either 0 or 100 g/ton. There were three pen replicates for each dose, resulting in six pens for each trial with at least 22 pigs per pen. The pen was the experimental unit. A randomized complete block design was used with location within a facility serving as the blocking factor. There were three location blocks in each trial. At each trial, three pens served as controls. Diagnosis of PPE was based upon clinical signs, gross lesions, and histopathologic confirmation of the presence of the organism.

c) Test Article Administration: The currently-marketed TYLAN® Type A medicated article was mixed in complete feed so that the final mixture contained 100 grams of tylosin per ton of feed. Tylosin was administered at 0 and 100g/ton in complete feed, fed ad libitum. Non-medicated acclimation feed was fed for at least 3 days prior to the test period. Test article was fed for 21 days.

d) Pertinent Variables Measured: Efficacy variables were daily individual Clinical Impression Scores (CIS); daily individual abdominal fill/distention scores; daily pen fecal scores; Average Daily Gain (ADG), Average Daily Feed (ADF), Feed to Gain (F/G) and Gain to Feed (G/F) ratios.

e) Result of Clinical Antemortem Variables: Clinical impression scores were collected on every animal every day for the entire study period. Scoring was conducted using a scale of 0 to 3, with 0 = normal, 1 = depression; 2 = moderate depression; and 3 = severe depression (moribund). Daily individual abdominal fill/distention scores were collected on every animal every day for the entire study period. Scoring was conducted using a scale of 0 to 3, with 0 = normal, 1 = slight gauntness, 2 = moderate gauntness; and 3 = severely gaunt). Daily pen fecal scores were recorded daily for the entire study period. Scoring was conducted using a scale of 0 to 3 with 0 = normal, 1 = pasty feces, 2 = watery feces, and 3 = diarrhea with blood). A comparison of pig

scoring trends across days for pigs medicated at 100 g/ton versus nonmedicated pigs shows the distribution of pigs in each category as very nearly the same at the beginning of the trial. As the trial progressed, the pigs receiving tylosin at 100 g/ton began returning to normalcy in a greater number and within an earlier time frame than the nonmedicated pigs. Most unmedicated pigs were not back to normal by the trial's end, whereas most of the pigs treated with 100 g/ton tylosin returned to normal by Day 10. The pooled averages of clinical disease measurements in the trials is summarized in Table 4.3.

Table 4.3. Averages of clinical antemortem variables

	Clinical Impression Score		Abdominal Fill Score		Pen Fecal Score	
Trial	0 g/ton	100 g/ton	0 g/ton	100 g/ton	0 g/ton	100 g/ton
T1X019503	0.77	0.35	0.77	0.35	1.24	1.00
T1X319505	0.23	0.07	0.35	0.13	0.92	0.13
T1X319506	0.22	0.05	0.40	0.13	0.54	0.05
T1X019508	0.40	0.22	0.40	0.22	1.10	1.00
Average of 4 sites	0.41	0.17	0.48	0.21	0.95	0.54

f) Results of Gain Variables: The data indicate that tylosin fed at 100 g/ton caused significant improvements in average daily gain, average daily feed, feed/gain, and gain/feed. The pooled analysis of the weight gain and feed efficiency measurements in the trials is summarized in Table 4.4.

Table 4.4. Pooled analysis of performance variables (means)

Group	ADG (lb/hd/day)	ADF (lb/head/day)	F/G	G/F
Tylosin 0 g/ton	0.823	2.415	2.911	0.345
Tylosin 100g/ton	1.008	2.670	2.648	0.385
Improvement (%)	23%	11%	9.1%	11%
p-value*	0.031	0.016	0.056	0.058M

* p-values are one-sided significance tests

g) Statistical Analysis: Average daily gain, average daily feed, feed/gain and gain/feed for pigs receiving 0 or 100 g/ton were analyzed using a mixed-model analysis in which TREATMENT was the fixed effect, and TRIAL, TRIAL x TREATMENT interaction, and BLOCK within trial were random effects. The results of the analysis are provided in Table 4.4. The p-values reported by the firm represent one-sided significance tests. The clinical disease variables were not analyzed statistically.

h) Conclusion: Feeding pigs tylosin at 100 g/ton for 21 days is effective for the prevention and/or control of PPE (ileitis).

i) Adverse Reactions: No adverse reactions were reported by the investigative team during or upon completion of this study.

III. TARGET ANIMAL SAFETY

The data upon which this application was approved are contained in NADA 12-491 for the original approval for TYLAN® premixes (See 26 FR 4359, dated May 19, 1961).

IV. HUMAN FOOD SAFETY

As described in 21 CFR 556.740, the current tolerance established for tylosin residues in the edible tissues of swine that have consumed the antibiotics is 0.2 part per million (negligible residue) in uncooked fat, muscle, liver, and kidney. As described in 21 CFR 558.625, tylosin phosphate has a zero-day pre-slaughter withdrawal period in swine.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR Part 514 of the implementing regulations. The data demonstrate that TYLAN® Type A medicated articles are effective for the prevention and/or control of porcine proliferative enteropathies (ileitis) in swine associated with Lawsonia intracellularis when administered in feed for 21 days at a level of 100 g/ton.

Under the Center's supplemental approval policy, 21 CFR 514.106(b)(2)(v) this is a Category II change. The approval of this change is based on new safety and effectiveness data provided with the application.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action is categorically excluded under 21 CFR 25.24(d)(1)(i) from the requirement to prepare an environmental assessment (EA). In considering this action, the Agency noted that the specific claim of proliferative ileitis is for an enteric disease that has been grouped with swine dysentery in the past. Therefore, the claim would have been previously treated under the more general indication of dysentery and the more specific claim of proliferative enteritis is not considered an expansion that would result in increased introduction of the drug into the environment. The categorical exclusion applies to this action because tylosin phosphate will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect. The data available to the Agency do not establish that, at the expected exposure level, the substance may be toxic to organisms in the environment.

Under Section 512(c)(2)(F)(iii) of the Act, this approval for food-producing animals qualifies for THREE (3) years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration

Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.