Date of Approval: November 13, 2008

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 012-491

TYLAN 40 and TYLAN 100

Tylosin phosphate
Type A medicated article
Swine

For the control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* immediately after medicating with TYLAN Soluble (tylosin) in drinking water.

Sponsored by:

Elanco Animal Health

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## I. GENERAL INFORMATION:

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|---|---|
| **A. File Number:** | NADA 012-491 |
| **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 Name:** | TYLAN 40 and TYLAN 100 |
| **D. Established Name:** | Tylosin phosphate |
| **E. Pharmacological Category:** | Antimicrobial |
| **F. Dosage Form:** | Type A medicated article |
| **G. Amount of Active Ingredient:** | 40 g/lb or 100 g/lb |
| **H. How Supplied:** | 50 lb bags |
| **I. How Dispensed:** | OTC |
| **J. Dosages:** | 40 to 100 grams (1.0 to 2.5 pounds of TYLAN 40) per ton of complete feed for 2 to 6 weeks immediately after medicating with 250 mg tylosin (as TYLAN Soluble) per gallon in drinking water for 3 to 10 days.<br><br>40 to 100 grams (0.4 to 1.0 pounds of TYLAN 100) per ton of complete feed for 2 to 6 weeks immediately after medicating with 250 mg tylosin (as TYLAN Soluble) per gallon in drinking water for 3 to 10 days. |
| **K. Route of Administration:** | Oral, in feed |
| **L. Species/Class:** | Swine |
| **M. Indication:** | For control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia* |

*intracellularis* immediately after medicating with TYLAN Soluble (tylosin) in drinking water.

**N. Effect of Supplement:** This supplement provides for the addition of a new indication for TYLAN Soluble (tylosin tartrate) followed by TYLAN Type A medicated article (tylosin phosphate) for the control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* in swine.

## II. EFFECTIVENESS:

### A. Dosage Characterization:

The dosage regimen tested for the control of porcine proliferative enteropathies (PPE, ileitis) was the currently approved dosage regimen for the use of tylosin in drinking water followed by tylosin in feed for the treatment and control of swine dysentery. This dosage regimen was selected because, while PPE and swine dysentery are caused by different pathogens, the two diseases share some clinical signs and are diagnosed under similar conditions. The effectiveness of tylosin in drinking water at 250 mg/gallon for 3 to 10 days followed by tylosin in feed at 40 to 100 grams per ton for 2 to 6 weeks for the treatment and control of swine dysentery was demonstrated for the approval of NADA 012-491 (TYLAN Type A medicated article) dated October 6, 1965 [30 FR 12730].

### B. Substantial Evidence:

**Type of Study: Dose Confirmation Model Study**

1) Title: "An Efficacy Dose Confirmation Study with TYLAN Soluble Powder Followed by TYLAN Premix for the Control of Porcine Proliferative Enteropathy (ileitis) in Swine." Study # T1XAM0501.
January 2007 to March 2007.

2) Investigators and Locations:
Terry TerHune, DVM, PhD, HMS, Veterinary Development Inc.,
Tulare, CA
Kelly Lechtenberg, DVM, PhD, Midwest Veterinary Services, Inc.,
Oakland, NE

3) Study Design:

a) *Objective*: To confirm the clinical effectiveness of tylosin tartrate administered in drinking water followed by tylosin phosphate, administered in

a Type C medicated feed for the control of porcine proliferative enteropathies (PPE, ileitis) in swine. This study was conducted in accordance with CVM Guidance for Industry 85, "Good Clinical Practice" (VICH GL9) May 9, 2001.

b) *Test Animals*: A total of 480 healthy, four to five week-old barrows and gilts were enrolled in this study. Pigs were obtained from separate swine sources for each study site. Animals weighed 11.4 to 28.6 pounds at enrollment, and originated from herds demonstrated to be free of *Lawsonia intracellularis* by polymerase chain reaction testing of random fecal samples prior to purchase.

c) *Experimental Design*: The study was conducted at two independent sites. A randomized complete block design was used at each site. The pen was the experimental unit. Treatment and control animals were not commingled in pens. Pens contained six pigs at the beginning of the study and there were 20 pens enrolled at each site.

On Day 0, all pigs were challenged with intestinal mucosal homogenate prepared from sections of affected pig intestine which were obtained from a recent, North American case of PPE. Pigs were dosed by gastric gavage to inoculate each pig with approximately $10^9$ *Lawsonia intracellularis* organisms.

d) *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**

| Group | Test Article | Dose/Route | Frequency/Duration |
|---|---|---|---|
| Treated | Tylosin tartrate<br><br>**Followed by:**<br>Tylosin phosphate | 250 mg tylosin/gallon of drinking water<br><br>40 g tylosin/ton in feed | *Ad libitum* for three days<br><br>*Ad libitum* for 14 days |
| Negative Control | Non-medicated water<br><br>**Followed by:**<br>Non-medicated feed | 0<br><br>0 | *Ad libitum* for three days<br><br>*Ad libitum* for 14 days |

e) *Test Article Administration*: Tylosin as the tartrate salt (TYLAN Soluble) was administered in the drinking water at 250 mg tylosin/gallon (65.8 ppm) for three days followed by tylosin as the phosphate salt (TYLAN Type A medicated article) administered in feed containing 40 g tylosin/ton for 14 days. Day X was defined as the day that 15% of the total population of study pigs at the study site were 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 (see score definitions below). Tylosin was administered in the drinking water from Day X + 1 through Day X + 3 and tylosin was administered in the feed from Day X + 4 through Day X + 17. Control pigs received no medication in water or feed for the duration of the study.

On Day X, four clinically affected pigs at each site were randomly 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.

f) *Measurements and Observations*: Pigs were observed twice daily. Animal health observations included observations for survival, general condition, and any abnormal clinical signs.

The primary variables were the percent abnormal pig days for each clinical score (diarrhea, abdominal gut fill, and pig attitude), mortality, lesion index, and average daily gain (ADG).

Clinical scores were evaluated daily from Day X + 1 through Day X + 17.

Diarrhea was described using the following clinical scoring scale.

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 was described using the following clinical scoring scale.

1 = Normal – Flank is full and rounded.
2 = Moderately gaunt – Flank is flat.
3 = Severely gaunt – Flank is very hollow.

Pig attitude was described using the following clinical scoring scale.

1 = Normal – Animal is bright, alert, and active, responding to stimuli.
2 = Slightly 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 number of days with an abnormal score (Score = 2 or Score = 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 through Day X+17 were weighed, necropsied, and considered "mortalities associated with PPE" if they had intestinal lesions consistent with PPE at necropsy (see scoring scale below).

On Day X + 18, all remaining pigs were weighed, euthanized, necropsied, and scored for PPE lesions according to the following criteria:

1 = Normal; no gross lesions
2 = Mild mesoserosal edema and hyperemia; a 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

The lesion index was defined 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 body weights (BW) by pen were recorded on Days -7, X, and X + 18. ADG was calculated for each pen by averaging the individual pigs' average daily gains within the pen. ADG for each individual pig was calculated by subtracting the study animal's weight on Day X from that same weight on Day X + 18 and dividing the result by 18.

At least one of the following sets of criteria had to be met in order to demonstrate effectiveness:

- At least two of the three clinical parameters were statistically significantly improved ($p \leq 0.05$) in the treated group compared to the control group –

AND – Mortality was not statistically significantly higher ($p \leq 0.05$) in the treated group compared to the control group.

**OR**

- The lesion index was statistically significantly improved ($p \leq 0.05$) in the treated group compared to the control group – AND – Average daily gain (ADG) was numerically higher in the treated group compared to the control group – AND – Mortality was not statistically significantly higher ($p \leq 0.05$) in the treated group compared to the control group.

g) *Statistical Analysis*: The criteria for substantial evidence of effectiveness required demonstration of effectiveness at each site, analyzed separately. For each of the clinical parameters (diarrhea score, abdominal gut fill score, pig attitude score) arcsine square root transformed percent of pig-days with abnormal scores (Score = 2 or Score = 3) was analyzed using a mixed effect linear model with treatment as a fixed effect and with block and residual as random effects. A one-sided comparison of tylosin versus negative control was conducted at the 0.05 significance level, with lower percent abnormal among treated groups considered favorable.

Percent mortality was compared between the two treatment groups using Fisher's Exact Test at the 0.05 level of significance.

4) Results: A total of 470 pigs completed the study.

a) *Clinical Scores*: At Site 1, abnormal pig days for gut fill was significantly improved in the treated group compared to the control group ($p = 0.0034$), and abnormal pig days for diarrhea was significantly improved in the treated group compared to the control group ($p = 0.0017$). Similarly, at Site 2, abnormal pig days for gut fill was significantly improved in the treated group compared to the control group ($p < 0.0001$), and abnormal pig days for diarrhea was significantly improved in the treated group compared to the control group ($p = 0.0001$). Significant differences in percent abnormal pig days for attitude were seen between control and treated groups at Site 1 ($p = 0.0011$) but not at Site 2 ($p = 0.2067$).

**Table 2. Percent Abnormal Pig-Days for Clinical Parameters[1]**

| Site | Treatment Group | Diarrhea[2] (%) | Pig Attitude[2] (%) | Gut Fill[2] (%) |
|---|---|---|---|---|
| 1 | Tylosin | 77.9[a] | 8.1[a] | 12.9[a] |
| | Control | 90.7[b] | 17.8[b] | 20.5[b] |
| 2 | Tylosin | 40.0[a] | 2.3[a] | 47.2[a] |
| | Control | 56.7[b] | 3.3[a] | 69.3[b] |

[1] Within each column at a given site, values with different superscripts indicate statistically significant differences between treatment and control groups ($p \leq 0.05$).

[2] Values are back-transformed from LSMeans.

b) *Mortality*: At each site, no significant increase in mortality was observed in the tylosin-treated group. At Site 1, percent mortality was 10.3% for control animals and 3.3% for tylosin-treated animals. At Site 2, percent mortality was 0% for both control and tylosin-treated animals.

c) *Lesion Index*: The lesion index for each pig was calculated as the sum of the lesion score multiplied by the associated lesion length. The average pen lesion index was then computed. Examination of the standard errors versus the means justified the use of the LOG+1 transformation. The lesion index differed significantly between control and tylosin-treated animals at Site 1 ($p < 0.0001$) but not at Site 2 ($p = 0.0549$). At Site 1, the back-transformed mean lesion index was numerically less in tylosin-treated animals (73) than in control animals (237). At Site 2, however, the back-transformed mean lesion index was numerically greater in tylosin-treated animals (180) than in control animals (122).

d) *ADG*: ADG was computed for each individual pig, and averaged across all pigs within a pen. At Site 1, ADG differed significantly ($p = 0.0007$) between tylosin-treated pens (0.25 kg/day) and control pens (0.19 kg/day). At Site 2, ADG was not significantly different ($p = 0.5156$) in the tylosin-treated pens (0.35 kg/day) compared to the control pens (0.33 kg/day).

e) *Secondary Variables*: Mean average daily feed intake (ADFI), mean feed to gain ratio (F/G), and mean pen total BW gain were examined at each site (Table 3). At Site 1, ADFI did not significantly change ($p = 0.1497$) in the tylosin-treated pens (0.59 kg feed/day) compared to the control pens (0.57 kg feed/day), F/G significantly decreased ($p = 0.0002$) in the tylosin-treated pens (2.46) compared to the control pens (3.43), and pen total BW gain significantly increased ($p < 0.0001$) in the tylosin-treated pens (27.3 kg) compared to the control pens (18.9 kg). At Site 2, ADFI did not significantly increase ($p = 0.4334$) in the tylosin-treated pens (0.64 kg/day) compared to the control pens (0.65 kg/day), F/G did not significantly decrease ($p = 0.1145$) in the tylosin-treated pens (1.89) compared to the control pens (1.97), and pen total BW gain did not significantly increase ($p = 0.4948$) in the tylosin-treated pens (35.8 kg) compared to the control pens (35.8 kg).

**Table 3. Secondary Variables[1]**

| Site | Treatment Group | Average Daily Feed Intake (kg/day)[2] | Feed/Gain[2] | Pen Total Weight Gain (kg)[2] |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 1 | Tylosin | 0.59[a] | 2.46[a] | 27.3[a] |
| | Control | 0.57[a] | 3.43[b] | 18.9[b] |
| 2 | Tylosin | 0.64[a] | 1.89[a] | 35.8[a] |
| | Control | 0.65[a] | 1.97[a] | 35.8[a] |

[1]Values with different superscripts within each column are statistically significant ($p \leq 0.05$).

[2]Values are LSMeans.

5) Adverse Reactions: No adverse reactions attributable to the test article were reported at either site.

6) Conclusions: Treated animals had statistically significant improvement in two of the three clinical parameters (abnormal pig days for gut fill and abnormal pig days for diarrhea) and mortality was not statistically significantly higher in the treated group compared to the control group. This study demonstrated that the use of tylosin tartrate, administered in drinking water at 250 mg tylosin/gallon (65.8 ppm) for three days followed by tylosin phosphate administered at 40 g tylosin/ton in feed for two weeks, was effective for the control of PPE (ileitis) in swine.

## 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 a summary 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:

#### 1. Summary of Residue Chemistry Studies

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.

#### 2. Target Tissue and Marker Residue Assignment

No marker residue or target tissue is specified for tylosin.

### 3. Tolerance Assignments

As described in CFR 556.740, a tolerance of 0.2 parts per million (negligible residue) is established for residues of tylosin in the uncooked edible tissues of swine.

### 4. Withdrawal Time

The product qualifies for a zero-day withdrawal period.

## C. Microbial Food Safety:

The Agency carefully considered the proposed addition of the indication, "for control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* immediately after medicating with TYLAN Soluble (tylosin) in drinking water," to the approved regimen of 250 mg/gal tylosin in drinking water for 3 to 10 days, followed by 40 to 100 g/ton tylosin in feed for 2 to 6 weeks in swine. The Agency determined that adding this indication to a previously approved regimen should not significantly impact public health, and 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 or TYLAN 100 Type A medicated article:

Warning: TYLAN 40 [TYLAN 100] may be irritating to unprotected skin and eyes. When mixing and handling TYLAN 40 [TYLAN 100] use protective clothing, impervious gloves, and a dust respirator. In 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.

Not for human use.

## 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 and TYLAN 100 Type A medicated article, when used according to the label, are safe and effective for the control of porcine proliferative enteropathies (PPE, ileitis) associated with *Lawsonia intracellularis* immediately after medicating with TYLAN Soluble (tylosin) in drinking water. Additionally, data demonstrate that residues in food products derived from swine treated with TYLAN 40 and TYLAN 100 Type A medicated article 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 the approval. The three years of marketing exclusivity applies only to the new claim for which this supplement is approved.

### 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)(1)).

### D. Patent Information:

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

## VII. ATTACHMENTS:

Facsimile Labeling:
TYLAN 40 Type A medicated article bag label
TYLAN 100 Type A medicated article bag label
Tylosin Ileitis Control Type B Medicated Swine Type B medicated feed label
Tylosin Ileitis Control Type B Medicated Swine Type C medicated feed label