Date of Approval: July 30, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 013-076

TYLAN Soluble

Tylosin Tartrate

Water Soluble Powder

Broiler Chickens

For the control of mortality caused by necrotic enteritis (NE) associated with *Clostridium perfringens* in broiler chickens.

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly & Co.

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I. GENERAL INFORMATION

A. File Number

NADA 013-076

B. Sponsor

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

Drug Labeler Code: 000986

C. Proprietary Name

TYLAN Soluble

D. Established Name

Tylosin tartrate

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Water soluble powder

G. Amount of Active Ingredient

100 grams tylosin base per jar

H. How Supplied

Jars containing tylosin tartrate equivalent to 100 grams tylosin base

I. Dispensing Status

Rx

J. Dosage Regimen

225 to 375 ppm (851 to 1419 mg tylosin per gallon) in drinking water for five consecutive days

K. Route of Administration

Oral in drinking water

L. Species/Class

Broiler chickens

M. Indication

For the control of mortality caused by necrotic enteritis (NE) associated with *Clostridium perfringens* in broiler chickens

N. Effect of Supplement

This supplement provides for the addition of the indication for the control of mortality caused by necrotic enteritis (NE) associated with *Clostridium perfringens* in broiler chickens.

II. EFFECTIVENESS

A. Dosage Characterization

The dose of 150 ppm was chosen for evaluation in the effectiveness study because published information suggested that this dose would be effective in controlling mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens. In one study, birds were administered 150 ppm tylosin tartrate in drinking water for five days after an outbreak of necrotic enteritis had been confirmed. The results showed that 150 ppm was effective for controlling mortality caused by necrotic enteritis. The abstract of this study was published in Poultry Science [see Brennan *et al*., Water-soluble tylosin tartrate (TYLAN Soluble Powder) for treatment of necrotic enteritis in broiler chickens, Poultry Science, Volume 80, Supplement 1:135, 2001].

B. Substantial Evidence

1. Multi-location field study in broiler chickens with induced necrotic enteritis.

a. Title: Study # T1Y060401: "Clinical Study: An Efficacy Dose Confirmation Study with TYLAN Soluble Powder for the Control of *Clostridium perfringens*-Related Mortality (Necrotic Enteritis) in Flocks of Growing Chickens." August 2007 to November 2007.

b. Study Investigators and Locations:

Terry TerHune, DVM, PhD, HMS Veterinary Development Inc., Tulare, CA

Heather S. Bruce, MS, PhD, and Ewen McMillan, DVM, MSc, Nutreco Canada Agresearch, Ontario, Canada

Michael Sims, BS, Virginia Diversified Research & Consulting LLC, Harrisonburg, VA

c. Study Design

1) *Objective:* To confirm the clinical effectiveness of tylosin administered at 150 ppm for five days in drinking water for the control of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens.

2) *Study Animals:* A total of 8,008 healthy, day-of-hatch straight run (males and females) birds were enrolled in this study. Birds were obtained from separate commercial hatcheries for each study site.

Birds were from breeder flocks that had not been vaccinated for necrotic enteritis. Birds were not vaccinated against coccidiosis.

3) *Experimental Design:* The study was conducted at three independent sites. A complete randomized block design was used at each site. The pen was the experimental unit. Treatment and control animals were not commingled in pens. There were 54 birds per pen (26 pens per treatment group) at Site 1, and 50 birds per pen (26 pens per treatment group) at Sites 2 and 3. On Day 0, all birds were challenged with an inoculum containing approximately 10^8 colony forming units (CFU) per mL of a *C. perfringens* isolate originating from a field case of necrotic enteritis in Canada. Birds were exposed to bacteria via feed commencing the afternoon of Day 0 and ending the morning of Day 1.

4) *Treatment Groups:* The two treatment groups used in this study were the test article treatment group (tylosin at 150 ppm [567.8 mg/gallon] in drinking water) and a negative control treatment group (non-medicated drinking water).

5) *Test Article Administration:* Tylosin as the tartrate salt was administered continuously in drinking water at 150 ppm (567.8 mg/gallon) for five consecutive days. Treatment was initiated on Day X, defined as any point after Day 0 when, cumulatively, at least 3% of the total population of study birds had died or been euthanized and three of six arbitrarily-selected dead birds were determined to have intestinal lesions consistent with a diagnosis of necrotic enteritis.

6) *Measurements and Observations:* Birds were observed twice daily for survival, general condition, and any abnormal clinical signs. *C. perfringens* was to be isolated from at least 30 study animals to confirm the adequacy of challenge.

   The primary variable for determining effectiveness was the proportion of mortality caused by necrotic enteritis for the test article and the negative control groups from Day X (initiation of treatment) to Day X+12 (end of the study). An animal was considered a study mortality caused by necrotic enteritis if death/euthanasia occurred following initiation of treatment AND the animal had a gross necropsy diagnosis of necrotic enteritis AND the animal had a necrotic enteritis lesion score ≥1.

   The entire small intestine was scored for necrotic enteritis lesions as follows:

   0 = Normal, no evidence of gross lesions.
   1 = Thin-walled, friable small intestine.
   2 = Focal necrosis and/or ulceration.
   3 = Multi-focal coalescing areas (large patches) of necrosis.
   4 = Severe extensive necrosis (typically seen in birds that have died from necrotic enteritis).

The small intestine was also scored for coccidiosis lesions as follows:

0 = No gross lesions.
1 = Small petechiae on serosa. May have small amounts of orange mucus.
2 = Numerous petechiae on serosa. Orange mucus may fill intestine. Thickened intestinal wall.
3 = Intestinal wall ballooned and thickened. Roughened mucosal surface. Intestinal contents filled with pinpoint blood clots and mucus.
4 = Intestinal wall ballooned for most of its length. Contains blood clots and digested blood giving characteristic color and putrid odor. Intestinal wall is greatly thickened.

A bird diagnosed with concurrent necrotic enteritis and coccidiosis was included in the data analysis as a study mortality caused by necrotic enteritis.

7) *Statistical Analysis:* Mortality caused by necrotic enteritis was represented as a binary response for each bird, where 0 = alive or death from a cause other than by *C. perfringens* and 1 = death caused by necrotic enteritis. In each pen, the arcsine square root transformed proportion (p) of birds dying from necrotic enteritis was analyzed using a mixed model with treatment as a fixed effect and with site, block (site), and site by treatment as random effects.

Evaluation of effectiveness was obtained from the test of the treatment main effect at the two-sided 0.05 level.

d. Results: Mortality caused by necrotic enteritis from Day X (initiation of treatment) to Day X+12 (end of study) was significantly different ($p = 0.0300$) between the test article group and control group birds with a lower mortality for the test article group birds, as shown in Table 1 below.

Table 1. Mortality caused by necrotic enteritis associated with *Clostridium perfringens*.

Treatment Group	Mortality (%)[1]
Tylosin	7.3
Control	32.0

[1] Values are back transformed from LS means.

e. Adverse Reactions: No adverse reactions attributable to the test article were reported at any of the three sites.

f. Conclusions: This study demonstrated that the use of tylosin as the tartrate salt, administered in the drinking water at 150 ppm (567.8 mg/gallon) for five days was effective for the control of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 012-648, as published in the FEDERAL REGISTER [26 FR 6544] on July 21, 1961, contains a summary of target animal safety studies for TYLAN Soluble in broiler chickens at 528 ppm (2 grams/gallon) as the sole source of drinking water for five days. NADA 012-648 was incorporated into NADA 013-076 on September 22, 1971.

IV. HUMAN FOOD SAFETY:

A. Microbial Food Safety (Antimicrobial Resistance):

The Agency evaluated microbial food safety data for TYLAN Soluble for control of mortality caused by necrotic enteritis (NE) associated with *Clostridium perfringens* in broiler chickens. The microbial food safety assessment submitted for Agency review included 1) a *release assessment* to describe the probability that tylosin tartrate and its use at a dose range from 225 to 375 ppm in drinking water for broiler chickens for five consecutive days will result in the emergence of resistant bacteria or resistance determinants in treated chickens under the proposed conditions of use, 2) an *exposure assessment* to describe the likelihood of human exposure to resistant bacteria or resistance determinants through consumption of edible products from treated chickens, and 3) a *consequence assessment* to describe potential human health consequences arising from exposure to defined resistant bacteria or resistance determinants by considering the human medical importance of antimicrobials (*e.g.*, macrolides) used in the treatment of human infectious diseases. Additionally, data from *in-vivo* studies designed to assess the potential for TYLAN Soluble when administered to chickens at the proposed conditions of use including the proposed dose range (225 to 375 ppm) to select for the development of macrolide-resistant *Campylobacter* were also submitted.

The risk assessment included information on tylosin tartrate, specifically its spectrum of antibacterial activity, mechanism(s) of macrolide resistance, and impact on the development or selection of antimicrobial resistance in foodborne pathogens of public health concern (*Campylobacter* and *Enterococcus)* as a result of the use of tylosin tartrate in chickens. Data from *in vivo* studies revealed that there was no selection of macrolide non-susceptible and/or resistant *Campylobacter* when broiler chickens were exposed to a dose of 225 ppm of tylosin tartrate in water for five days. Therefore, based on data from the sponsor's *in-vivo* studies, including information previously reviewed and the sponsor's microbial food safety risk assessment, the Agency concluded that administration of tylosin tartrate at 225 ppm, including concentrations above 225 ppm, should not adversely impact human health with respect to selection or emergence of macrolide-resistant *Campylobacter* originating from broiler chickens treated with tylosin tartrate for five days. Gram negative organisms of human health importance, such as *Escherichia coli* and *Salmonella,* were not considered a hazard in this risk assessment, as they are intrinsically resistant to macrolides.

In summary, based upon the Agency's evaluation of the information submitted by the sponsor, and in consideration of the spectrum of activity of tylosin tartrate, including the potential of tylosin tartrate to select for emergence of antimicrobial resistance in bacteria of public health concern in or on treated chickens, including the prevalence of *Campylobacter* and *Enterococcus* in chicken-derived food products, and taking into consideration the following conditions of use for tylosin tartrate in drinking water for broiler chickens:

- TYLAN Soluble (tylosin tartrate) will be administered by prescription (Rx) only;
- Only broiler chickens from flocks with a diagnosis of necrotic enteritis (*e.g.*, increased mortality and lesions characteristic of necrotic enteritis upon necropsy) will be administered TYLAN Soluble;
- TYLAN Soluble will be administered at a dose range from 225 to 375 ppm for 5 days in the drinking water of broiler chickens and will have no refills;
- Once initiated, the full dose and dosing regimen of TYLAN Soluble should be administered;
- Use of TYLAN Soluble or another macrolide is not advised if additional therapy is needed beyond the original course of medication;
- Resistance to macrolides is monitored by FDA's post-approval National Antimicrobial Resistance Monitoring System (NARMS) program;

the Agency considers that use of tylosin tartrate for the control of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens, will not result in a significant risk to the development of macrolide resistance in foodborne *Campylobacter* and/or *Enterococcus* originating from treated broiler chickens. The overall risk estimation associated with the use of tylosin tartrate in drinking water for broiler chickens under the proposed conditions of use is high, based on individual rankings of medium for the *release assessment*, high for the *exposure assessment,* and high for the *consequence assessment*. The latter ranking of high for the *consequence assessment* is based on macrolides being critically important in human medicine, because they are the drug of choice to treat confirmed cases of campylobacteriosis, especially in children where there are safety concerns about the use of fluoroquinolones. However, the Agency considers that administration of tylosin tartrate under the supervision of a veterinarian, limited to a single 5-day treatment in broiler chickens, including the potential re-treatment of necrotic enteritis in the same flock (treated once with tylosin tartrate) with a non-macrolide ensures that the overall extent of use of additional macrolide therapies in broiler chickens receiving treatment with tylosin tartrate is adequately limited. The Agency therefore concludes that the proposed conditions of use and appropriate label restrictions outlined above are adequate to support the use of tylosin tartrate in drinking water for broiler chickens, and help to ensure that risks to public health from macrolide-resistant *Campylobacter* and/or *Enterococcus* originating from treated broiler chickens are minimal.

Decision Statement:

The Agency's evaluation of information to address microbial food safety risks associated with the proposed use of TYLAN Soluble resulted in an overall risk estimation of high; therefore, administration of tylosin tartrate under the supervision of a veterinarian, limited to a single 5-day treatment in broiler chickens, including the potential re-treatment of necrotic enteritis in the same flock (treated once with tylosin tartrate) with a non-macrolide ensures that the overall extent of use of additional macrolide therapies in chickens receiving treatment with tylosin tartrate is adequately limited. These conditions of use and corresponding label restrictions support the safe use of tylosin tartrate in drinking water for broiler chickens, and help to ensure that risks to public health from macrolide-resistant *Campylobacter* and/or *Enterococcus* originating from treated broiler chickens have been mitigated.

B. Impact of Residues on Human Intestinal Flora:

1. Determination of the need for establishing a microbiological ADI (acceptable daily intake)

a. Step 1: Are residues of tylosin and/or its metabolites microbiologically active against representative human intestinal bacteria?

The sponsor performed an *in vitro* susceptibility testing study and concluded that tylosin is active against representative bacteria from the human intestinal tract. The study is summarized below.

Study Title: Activity of tylosin against bacterial strains representing the normal human intestinal microbiota: determination of Minimum Inhibitory Concentration (MIC).

Study Number: DWS: P1/039/05

Study Period: February 27, 2006, to October 17, 2006

Study Director: Dr. Andrew Pridmore

Study Location: Don Whitley Scientific Limited, Shipley, West Yorkshire BD17 7SE United Kingdom

Study Design: The objective of the study was to determine the MIC of tylosin against representative human intestinal bacteria. MICs of tylosin were determined against 10 isolates from 10 bacterial groups, which were obtained from the feces of healthy, unmedicated human volunteers. *Bacteroides fragilis* ATCC 25285, *Eubacterium lentum* ATCC 43055, and *Staphylococcus aureus* ATCC 29213 were used as quality control strains. Agar dilution was used, and testing conditions and inoculum were based on recommendations from the Clinical and Laboratory Standard Institute (CLSI).

Results and Conclusions: MIC_{50}, MIC_{90}, MIC range, and geometric MIC were determined for each group. Among bacterial groups tested, tylosin did not show activity against any of the isolates of *E. coli*. However, the compound was active against all other bacterial groups. The most

susceptible groups were Gram-positive anaerobes, such as *Bifidobacterium*, *Clostridium*, *Eubacterium*, and *Peptostreptococcus*. MIC-related information is shown in Table 2 below. Excluding *E. coli*, a MIC_{calc} is calculated to be 0.237 µg/mL.

Table 2. Susceptibility of tylosin against representative human intestinal bacterial groups.

Bacterial Group (10 isolates from each group)	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Geometric MIC (µg/mL)
Bacteroides fragilis	0.5 - 128	1	32	2.6
Bacteroides (others)	0.25 - 32	0.5	32	1.3
Bifidobacterium	0.031 - 2	0.062	1	0.12
Clostridium	0.031 - 0.5	0.062	0.25	0.094
Enterococcus	1 - 4	1	4	2.0
Escherichia coli	All > 128	>128	>128	>128
Eubacterium	0.125 - 1	0.25	0.5	0.31
Fusobacterium	0.062 - 64	1	4	1.5
Lactobacillus	0.5 - 8	2	8	2.0
Peptostreptococcus	0.125 – 0.5	0.5	0.5	0.41
All strains (n = 100)	0.031 - >128	0.5	>128	1.2

b. Step 2: Do residues of tylosin and/or its metabolites enter the human colon?

Yes, tylosin residues are able to enter the human colon. Findings from earlier radiolabeled residue depletion studies revealed that only a small quantity could enter the colon by consumption of chicken tissues under proposed conditions.

The following is a summary of the analysis:

- Calculations were on the consumption of liver, which is the tissue with the highest concentration of tylosin residues, representing a worst case scenario;
- When radiolabeled tylosin was fed to chickens at 528 ppm every day for 3 days there was very low radioactive material in the liver;
- The concentration of the marker residue (tylosin A) and the biologically active metabolite (tylosin D) were below a limit of detection (LOD) of 0.01 µg/g. No tylosin residues were detected after 1-day of withdrawal in chickens fed 500 ppm of tylosin for 8 days. The LOD of the method was 0.02 µg/g, which was used as the tissue concentration;
- A person consuming 100 grams of chicken liver containing 0.02 µg/g would ingest 2 µg of tylosin residues;
- The metabolism of tylosin in humans is unknown because it is not an approved drug for use in humans. However, a metabolism study

performed in swine fed radiolabeled tylosin for 5 days showed that the drug was heavily metabolized. No more than 15% of the original dose was excreted into the feces daily.

- Thus, 15% of 2 µg, or 0.3 µg of tylosin could enter the colon of a person consuming liver from chickens treated with 528 ppm of tylosin for 5 days with a 1-day withdrawal time.

- In a worst case scenario and using an even more conservative approach, if the concentration was doubled to 30% of the total dose, a maximum of tylosin residues reaching the human colon after the consumption of 100 grams of chicken liver would be in a total of 0.6 µg.

c. Step 3: Do residues of tylosin and/or its metabolites entering the colon remain microbiologically active?

The sponsor concluded "yes" from the data from a fecal-binding study. The study demonstrated that there are 30% of tylosin residues in the colon bound to feces, and 70% remaining biologically active. Details of the study are summarized below.

Study Title: Effect of fecal binding on the antibacterial activity of tylosin

Study Number: DWS: P1/040/05

Study Period: April 3, 2006, to May 6, 2006

Study Director: Dr. Andrew Pridmore

Study Location: Don Whitley Scientific Limited, Shipley, West Yorkshire BD17 7SE United Kingdom

Study Design: The studies were performed according to the Organization for Economic Co-operation and Development (OECD) principles of good laboratory practices as set forth by the United Kingdom. The objective of the studies was to determine the effect of fecal binding on the antimicrobial activity of tylosin. Tylosin concentrations tested were at 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.4, 2.7, 3.0, and 3.3 µg/mL, in Mueller Hinton broth (MHB). Each drug concentration was mixed with fecal samples from three healthy human volunteers at concentrations of 0 (MHB only), 25%, and 50%, and incubated continuously for 12 hours at 37 °C. The reference bacterial strain was *Enterococcus faecalis* (ATCC 28212) that is susceptible to tylosin. Inoculum was prepared using the McFarland Standard No. 0.5 at a final density of approximately 5×10^5 colony-forming units.

Following incubation, supernatants of the mixes were inoculated with a suspension of *E. faecalis* and incubated for 24 hours. The antibacterial activity of the supernatants obtained from each of the incubation times (*i.e.*, 0, 1, 2, 6, 8, and 12 hours) was assessed by the presence or absence of bacterial growth after incubation of the suspension in the microtiter plates. The differences in antibacterial activity before and after incubation with feces were used to calculate the percentage of tylosin bound to feces.

The bound proportion of tylosin to fecal material was estimated by the following formula:

> % bound = [(Concentration of inhibition in feces - concentration of inhibition in broth)/concentration of inhibition in feces] x 100

Results and Conclusions: The lowest tylosin concentration that prevented *E. faecalis* growth in the absence of feces (0%) was between 1.2 and 1.5 µg/mL. This concentration remained constant for the 12-hour testing period. In the presence of 25% feces, the initial tylosin concentration necessary to prevent growth in the first hour increased. In the majority of the experiments, the tylosin concentration necessary to prevent growth increased as the incubation time increased beyond one hour. Maximal binding of tylosin to 25% feces occurred between 1 and 6 hours with binding ranging from 28.6% to 42.9%. With a suspension containing 50% of feces, binding (about 30%) was similar to that observed with 25% of feces.

The study findings concluded that tylosin binds to human fecal material. In the presence of 25% or 50% of feces, between 28.6% and 42.9% of tylosin were bound to feces. This binding was time-dependent, not fecal concentration-dependent. Due to practical limitations, it was impossible to perform *in vitro* studies with fecal concentrations exceeding 50%. Therefore, 50% is thought to give the closest *in vitro* representation of an *in vivo* situation with respect to the binding of tylosin residues to intestinal contents. It was estimated that tylosin binding to undiluted fecal material would occur between 1 and 6 hours and would probably be around 30%; therefore, 30% fecal binding is determined for the compound.

d. Step 4: Determination if there is any scientific justification to eliminate testing for either one or both endpoints of concern.

There are scientific justifications to eliminate testing of both endpoints of concern. It was concluded that the concentration of tylosin residues reaching the human colon is too low to affect the microbiota, based on the following findings:

According to the total residue data shown above, 0.3 to 0.6 µg of tylosin residues enter the colon;

Assuming a colonic mass of 220 grams, the final concentration of tylosin-derived residues in the colon would be 1.4 to 2.8 ng/gram of colon contents;

Considering that fecal binding of tylosin at a rate of 30%, a biologically active concentration of tylosin residues would be maximally 2.0 ng/gram;

- The MIC_{calc} is 0.24 µg/mL. Thus, the microbiologically active residue concentration is >100-fold lower than the average MIC for relevant, representative intestinal flora. Even for the group with the lowest MIC_{50} (at 0.06 µg/mL), it is >30-fold lower.

- Considering all of these points, it is unlikely that such tylosin residues would have meaningful impact on the human intestinal flora.

Decision Statement:

The amount of tylosin residues reaching the human colon and remaining microbiologically active is negligible, and is not expected to adversely affect human intestinal flora. Therefore, there is no need to determine a mADI for the proposed use.

C. Toxicology:

CVM did not require additional toxicology studies for this supplemental approval. The original approval for use of tylosin in broiler chickens under NADA 012-585, as published in the FEDERAL REGISTER [26 FR 6544] on July 14, 1961, contains all the toxicology studies.

D. Assignment of the Final ADI:

A toxicological acceptable daily intake (ADI), a microbiological ADI, or a final ADI for total residues of tylosin is not established.

E. Safe Concentrations for Total Residues:

Safe concentrations for total residues of tylosin in edible tissues are not determined. CVM concluded that, based on the data derived from the toxicology studies, the established tolerance of 0.2 parts per million for the presence of tylosin residues in the uncooked edible tissues in chickens would ensure safety to human consumers.

F. Residue Chemistry:

1. Summary of Residue Chemistry Studies

CVM did not require residue chemistry studies for this supplemental approval. The original approval of NADA 012-585 as published in the FEDERAL REGISTER [26 FR 6544] on July 14, 1961, contains a summary of residue chemistry studies for chickens.

2. Target Tissue and Marker Residue

No marker residue or target tissue is specified for tylosin.

3. Tolerance

As described in 21 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 chickens.

4. Withdrawal Time

As described in 21 CFR 520.2640, a 24-hour withdrawal time is established for use of tylosin in the drinking water of chickens.

G. Analytical Method for Residues:

The original approval of NADA 012-585 as published in the FEDERAL REGISTER [26 FR 6544] on July 14, 1961, contains analytical method summaries for tylosin in chickens.

V. USER SAFETY:

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

Mixing Directions for Medicated Drinking Water: Always add the water to the powder. Do not pour the powder into the water. Prepare a fresh TYLAN Soluble solution every three days. When mixing and handling tylosin, use protective clothing and impervious gloves.

Warnings

User Safety Warnings: Not for Human Use. Keep Out of Reach of Children. Avoid contact with human skin. Exposure to tylosin may cause a rash.

To report suspected adverse events, for technical assistance, or to obtain a Material Safety Data Sheet (MSDS), call 1-800-428-4441.

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 Soluble, when used according to the label, is safe and effective for the control of mortality caused by necrotic enteritis (NE) associated with *Clostridium perfringens* in broiler chickens. Additionally, data demonstrate that residues in food products derived from species treated with TYLAN Soluble will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because (a) professional expertise is required to appropriately diagnose and subsequently use this product to control necrotic enteritis and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

B. Exclusivity:

This supplemental approval for TYLAN Soluble qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental approval included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the indication "for the control of mortality caused by necrotic enteritis (NE) associated with *Clostridium perfringens* in broiler chickens".

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:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.