Approval Date: September 4, 2002

# FREEDOM OF INFORMATION SUMMARY

# ORIGINAL NEW ANIMAL DRUG APPLICATION

# NADA 141-198

## Tylosin (Tylan®) plus Salinomycin (Bio-Cox®)

**For increased rate of weight gain and improved feed efficiency, and as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix, E. acervulina*, *E. maxima, E. brunetti*, and *E. mivati* in broiler chickens.**

**Sponsored by:**

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

**FREEDOM OF INFORMATION SUMMARY**

Combined use of Tylan® and Bio-Cox® in Broiler Chicken Feeds

## 1. GENERAL INFORMATION:

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| a. File Number: | NADA 141-198 |
| 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. Established Names: | Tylosin phosphate<br>Salinomycin sodium |
| d. Proprietary Names: | Tylan®<br>Bio-Cox® |
| e. Dosage Form: | Type A medicated articles |
| f. How Supplied: | Tylan® 50 lb. bags<br>Bio-Cox® 50 lb. bags |
| g. How Dispensed: | OTC |
| h. Amount of Active Ingredients: | Tylosin: 10, 40 or 100 grams of tylosin activity per pound.<br>Salinomycin: 30 or 60 grams of salinomycin activity per pound. |
| i. Route of Administration: | These drugs are administered orally by adding the Type A medicated articles to complete broiler chicken feed (Type C medicated feed). |
| j. Species/Class: | Broiler chickens |
| k. Recommended Dosage: | Tylosin - 4 to 50 g/ton<br>Salinomycin - 40 to 60 g/ton |
| l. Pharmacological Category: | Antibiotic and anticoccidial |

| | |
|---|---|
| m. Indications: | For increased rate of weight gain and improved feed efficiency, and as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix, E. acervulina*, *E. maxima, E. brunetti*, and *E. mivati* in broiler chickens. |

**CAUTION:** For broiler chickens only. Do not feed to laying hens. Not approved for use with pellet binders. May be fatal if accidentally fed to adult turkeys or horses.

## 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 animal 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 Agency finds that the NADA 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.

Tylosin, as provided by Elanco Animal Health, has previously been separately approved for increased rate of weight gain and improved feed efficiency in chickens (21 CFR 558.625(f)(l)(iii)). Salinomycin, as provided by Alpharma Inc., has previously been separately approved for use in broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix, E. acervulina*, *E. maxima, E. brunetti*, and *E. mivati* in broiler chickens (21 CFR 558.550(d)(1)(b)). Effectiveness for each drug, tylosin and salinomycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 12-491 and Alpharma's NADA 128-686 (to which Elanco Animal Health has a right of reference), respectively. Because tylosin and salinomycin each have at least one use that is different from the other animal drug used in the combination, the NADA must also demonstrate that tylosin plus

salinomycin provide appropriate concurrent use for the intended target population. The use of tylosin plus salinomycin provides appropriate concurrent use because these drugs are intended to treat different conditions (tylosin, performance; salinomycin, coccidiosis) likely to occur simultaneously with sufficient frequency in broiler chickens. Salinomycin is not considered to be an antibacterial animal drug for such use in broiler chickens for the purposes of Section 512(d)(4) of the FFDCA, because salinomycin is approved only for prevention of a protozoal disease (coccidiosis) in broiler chickens.

## 3. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination in animal 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 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

- a scientific issue is 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.

Tylosin, as provided by Elanco Animal Health, has previously been separately approved for increased rate of weight gain and improved feed efficiency in chickens (21 CFR 558.625(f)(l)(iii)). Salinomycin, as provided by Alpharma Inc., has previously been separately approved for use in broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix, E. acervulina*, *E. maxima, E. brunetti*, and *E. mivati* in broiler chickens (21 CFR 558.550(d)(1)(b)). Target animal safety for each drug, tylosin and salinomycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 12-491 and Alpharma's NADA 128-686, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of tylosin or salinomycin when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety studies are required for approval of NADA 141-198.

## 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 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 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. Toxicity:

Safety of this combination product has been established by data in NADA 12-491 for tylosin and NADA 128-686 for salinomycin.

B. Tolerances for Residue:

For tylosin, a tolerance of 0.2 ppm (negligible residue) in uncooked fat, muscle, liver, and kidney in chickens has been previously codified under 21 CFR 556.740.

C. Residue Data:

Residue data supporting the approved uses tylosin and salinomycin, each having zero withdrawal times, were submitted to their respective original applications (see Toxicity, above). The following study, Elanco Study No. T1X700001, was conducted at Ricerca LLC, Painesville, OH, to establish that the depletion of each drug in the presence of the others is not affected and that the presence of the drugs in the same broiler tissue did not interfere with the assay of the drugs. In addition to providing data for the two-way combination product, the results of this study were used to support the three-way combination product, tylosin plus salinomycin plus roxarsone, in broiler chickens.

Cornish broiler chickens, approximately 3 weeks of age, were allocated to two control groups and two treatment groups. Test birds were allowed *ad libitum* access to medicated feed with 50 g/ton tylosin, 60 g/ton salinomycin, and 45.4 g/ton roxarsone for three weeks. Control birds were fed unmedicated basal ration *ad libitum*. Test birds were euthanized at zero (6 hrs), 24, 72, and 120 hours withdrawal. Control birds were euthanized at zero withdrawal. Liver (minus gall bladder) and skin with adhering fat were collected from each bird as appropriate for residue assay. The official microbiological methods were used to detect tylosin residues in the liver. Arsenic residues in livers were determined by a validated version of the regulatory AOAC method. Salinomycin residues in skin with adhering fat were determined by a validated method used in BioClin Study ANA-M0914-004.

Residues of tylosin in liver were below the tolerance level at zero withdrawal. Residue levels of salinomycin in skin with adhering fat were below the research tolerance of 0.2 ppm. These data indicate the absence of interference in the depletion pattern of the individual drugs. Therefore the data support assignment of a zero withdrawal time for the two-way combination, tylosin plus salinomycin.

Samples of control liver and control skin with adhering fat were fortified with tylosin, salinomycin, and roxarsone. The data showed that the presence of tylosin and roxarsone did not interfere with the assay of salinomycin, and that the presence of roxarsone and salinomycin did not interfere with the assay of tylosin. A non-interference study for roxarsone was not necessary because the assay method for roxarsone is done by ashing the tissue prior to determination of the roxarsone residues.

D. Regulatory Methods for Residues:

The regulatory method for detection of residues of tylosin phosphate is a microbiological test using *Micrococcus luteus* (ATCC 9341) as the test organism. This method is on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

## 5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the FFDCA and 21 CFR Part 514 of the implementing regulations. Tylosin (4 to 50 g/ton)

plus salinomycin (40 to 60 g/ton) are safe and effective for the claims indicated in section 1 of this FOI Summary.

Pursuant to 21 CFR 514.106(b)(2), this combination 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 this product, adequate directions of use by the layman have been provided and the product will have over-the-counter (OTC) status. Label directions provide detailed instruction in plain language. The drug products are not controlled substances. Thus, the combination is assigned OTC status, and the labeling is adequate for the intended use.

**6. ATTACHMENTS**:

Facsimile Labeling is attached as indicated below:

Type C Medicated Feed (Blue Bird) - Broiler chickens

Net weight lb (kg) on bag or bulk

# Tylosin/Salinomycin Broiler Chicken Ration

## Type C Medicated Feed

For increased rate of weight gain and improved feed efficiency, and as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix, E. acervulina*, *E. maxima, E. brunetti*, and *E. mivati* in broiler chickens.

### Active Drug Ingredient

Tylosin phosphate……4 to 50 g/ton
Salinomycin sodium……40 to 60 g/ton

### Guaranteed Analysis

Crude Protein, not less than……_____%
Lysine, not less than……_____%
Methionine, not less than……_____%
Crude Fat, not less than……_____%
Crude Fiber, not more than……_____%
Calcium, not less than……_____%
Calcium, not more than……_____%
Phosphorus, not less than……_____%
Salt[1], not less than……_____%
Salt[1], not more than……_____%
Sodium[2], not less than……_____%
Sodium[2], not more than……_____%

[1]If added.
[2]Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

### Ingredients

Each ingredient must be specifically named in accordance with the names and definitions adopted by the Association of American Feed Control Official's Publication.

### Directions for Use

Feed continuously as sole ration.

(OVER)

**CAUTION:** For broiler chickens only. Do not feed to laying hens. Not approved for use with pellet binders. May be fatal if accidentally fed to adult turkeys or horses.

**MANUFACTURED BY**

BLUE BIRD FEED MILL
Anytown, USA 12345