Date of Approval: December 30, 2019

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 013-076

Tylan™ Soluble

tylosin tartrate

Powder for solution

Honey bees

This supplement provides for the establishment of a tolerance of 500 parts per billion (ppb) for residues of tylosin in honey.

Sponsored by:

Elanco US Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 013-076

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Tylan™ Soluble

D. Drug Product Established Name

Tylosin tartrate

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Powder for solution

G. Amount of Active Ingredient

Tylosin tartrate equivalent to 100 grams (3.53 oz) tylosin base

H. How Supplied

100 gram bottle

I. Dispensing Status

Rx

J. Dosage Regimen

200 mg tylosin per colony mixed with 20 grams of confectioners sugar applied (dusted) over the top bars of the brood chamber once weekly for 3 weeks.

K. Route of Administration

Oral

L. Species/Class

Honey bees

M. Indication

For the control of American Foulbrood (*Paenibacillus larvae*).

N. Effect of Supplement

This supplement provides for the establishment of a tolerance of 500 ppb for residues of tylosin in honey.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the supplemental approval of NADA 013-076 dated October 17, 2005, contains dosage characterization information for the use of 200 mg tylosin per honey bee colony once weekly for 3 weeks.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 013-076 dated October 17, 2005, contains a summary of studies that demonstrate effectiveness of the drug for the use of 200 mg tylosin per honey bee colony once weekly for 3 weeks.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 013-076 dated October 17, 2005, contains a summary of target animal safety studies for the use of 200 mg tylosin per honey bee colony once weekly for 3 weeks.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety (Antimicrobial Resistance)

Because the effect of this supplement was to publish a tolerance for residues of tylosin in honey, no new information or data on the impact of the use of tylosin in honey bees on development of antimicrobial resistance among bacteria of public health concern in honey from treated bees was required.

B. Toxicology

Because the effect of this supplement was to publish a tolerance for residues of tylosin in honey, reassessment of the toxicology studies or information for tylosin was not needed for this supplemental approval. The FOI Summaries for the supplemental approvals of NADA 013-076, dated October 17, 2005, November 13, 2008, and July 20, 2014, contain toxicology studies supporting the human food safety of tylosin.

C. Safe Concentrations for Total Residues in Edible Tissues

Reassessment of the safe concentrations for total residues of tylosin for muscle, liver, kidney, fat, milk, and eggs was not needed for this supplemental approval. The safe concentration of total residues of tylosin in individual edible tissues of cattle, swine, chickens, and turkeys is 0.2 parts per million (ppm) for liver, kidney, fat, and muscle. The safe concentration of total residues of tylosin for milk is 0.05 ppm. The safe concentration of total residues of tylosin in eggs is 0.02 ppm.

The USA FDA has not assigned an acceptable daily intake (ADI) for total residues of tylosin. Therefore, the safe concentration for total residues of tylosin in honey is calculated obtaining a mean ADI from the ADI established by the European Medicines Agency (EMA) (6 µg/kg bw/day) and the Joint Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) Expert Committee on Food Additives (JECFA) (30 µg/kg bw/day) and using 1% of the mean ADI value and a food consumption value of 20 g for honey:

$$\text{Safe Concentration} = \frac{1\%\ \text{ADI} \times \text{Human Body Weight}}{\text{Food Consumption Value}}$$

$$= \frac{1\% \text{ x } 18\ \mu\text{g/kg bw/day x } 60\ \text{kg}}{20\ \text{g/day}}$$

$$= 540\ \mu\text{g/kg}$$

The number is rounded down to 500 µg/kg (500 ppb).

D. Residue Chemistry

1. Summary of Residue Chemistry Study

   Residues of tylosin resulting from various dosing schemes in honey are summarized in Table 1 (brood chamber honey) and Table 2 (surplus honey).

   Table IV.1. Mean concentrations (in ppm) of tylosin in brood chamber honey (lower, upper 95% confidence limits).

Treatment	7 days after final treatment	14 days after final treatment	21 days after final treatment
200 mg	1.45 (0.66, 3.46)	0.47 (0.21, 1.04)	0.40 (0.17, 0.88)
1000 mg	5.55 (2.20, 17.46)	4.52 (1.39, 4.31)	1.98 (0.87, 4.90)
0 mg	0.12 (0.03, 0.31)	0.00 (0.00, 0.06)	0.00 (0.00, 0.03)

Table IV.2. Mean concentrations (in ppm) of tylosin in surplus honey (lower, upper 95% confidence limits).

Treatment	0 day (on treatment)	7 days after final treatment	14 days after final treatment	21 days after final treatment
200 mg	1.30 (0.59, 3.06)	0.39 (0.17, 0.85)	0.33 (0.14, 0.73)	0.16 (0.05, 0.38)
1000 mg	8.73 (3.21, 34.27)	3.57 (1.50, 9.90)	2.46 (1.07, 6.33)	1.61 (0.72, 3.85)
0 mg (control)	0.05 (0.0, 0.16)	0.00 (0.00, 0.06)	0.0 (0.00, 0.07)	0.05 (0.00, 0.17)

We note that the EMA ADI results in a calculated tolerance (180 ppb) that is too low relative to the incurred residues seen in the field study. We note that the JECFA ADI results in a calculated tolerance (900 ppb) that is higher than needed relative to the incurred residues seen in the field study.

Based on the incurred residues seen in the field trials at 21 days post-treatment for the 200 mg dosing, a tolerance of 500 µg tylosin/kg (500 ppb) honey is assigned. The proposed tolerance assignment is consistent with the upper 95% confidence limit residue value and approximately mid-way between the tolerances that would be calculated using the EMA and JECFA ADIs.

2. Target Tissue and Marker Residue

   The target tissue is honey. The marker residue is parent tylosin.

3. Tolerances

   A tolerance of 500 ppb is established for residues of tylosin in honey.

4. Withdrawal Period

   Treatments should be completed at least four weeks prior to main honey flow.

E. Analytical Method for Residues

The analytical method for the detection of residues of tylosin in honey used in the residue study is a microbiological assay using an oxytetracycline-resistant strain of *Paenibacillus larvae* (the causative agent of American foulbrood disease of honey bees). To obtain a copy of the analytical method, please submit a Freedom of Information Summary request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest.requestinfo.cfm.

V. USER SAFETY

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

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.

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 (FD&C 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 American Foulbrood (*Paenibacillus larvae*) in honey bees. 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 order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, and because restricting this drug product to use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product in animals in order to slow or prevent any potential for the development of bacterial resistance to antimicrobial drugs.

B. Exclusivity

Tylan™ Soluble, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C Act.

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.