

Date of Approval: December 30, 2019

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 008-622

Terramycin[®]
Terramycin[®] Soluble Powder Concentrate
Terramycin-343[®]

Oxytetracycline hydrochloride

Powder for Solution

Honey bees

This supplement provides for the establishment of a tolerance of 750 parts per billion (ppb) for the sum of tetracycline residues in honey.

Sponsored by:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION	3
II. EFFECTIVENESS.....	4
A. Dosage Characterization	4
B. Substantial Evidence	4
III. TARGET ANIMAL SAFETY	4
IV. HUMAN FOOD SAFETY	5
A. Microbial Food Safety	5
B. Toxicology	5
C. Safe Concentrations for Total Residues in Edible Tissues.....	5
D. Residue Chemistry	5
E. Analytical Method for Residues	7
V. USER SAFETY	7
VI. AGENCY CONCLUSIONS	8
A. Marketing Status.....	8
B. Exclusivity.....	8
C. Supplemental Applications	8
D. Patent Information.....	8

I. GENERAL INFORMATION

A. File Number

NADA 008-622

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Terramycin®
Terramycin® Soluble Powder Concentrate
Terramycin-343®

D. Drug Product Established Name

Oxytetracycline hydrochloride

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Powder for solution

G. Amount of Active Ingredient

Terramycin®: 25 grams oxytetracycline hydrochloride (HCl)/lb

- 6.25 grams oxytetracycline HCl per 4 oz packet
- 10 grams oxytetracycline HCl per 6.4 oz packet
- 25 grams oxytetracycline HCl per 1 lb packet

Terramycin® Soluble Powder Concentrate: 102.4 grams oxytetracycline HCl/lb

- 25.6 grams oxytetracycline HCl per 4 oz packet
- 102.4 grams oxytetracycline HCl per 16 oz packet

Terramycin-343®: 343 grams oxytetracycline HCl/lb

- 51.2 grams oxytetracycline HCl per 2.39 oz packet
- 102.4 grams oxytetracycline HCl per 4.78 oz packet
- 204.8 grams oxytetracycline HCl per 9.55 oz packet
- 771.7 grams oxytetracycline HCl per 2.25 lb tub
- 1543.5 grams of oxytetracycline HCl per 4.5 lb tub

H. How Supplied

Terramycin®: 4 and 6.4 oz packets; 1 lb packet

Terramycin® Soluble Powder Concentrate: 4 and 16 oz packets

Terramycin-343®: 2.39, 4.78, and 9.55 oz packets; 2.25 and 4.5 lb tubs

I. Dispensing Status

Rx

J. Dosage Regimen

200 mg oxytetracycline HCl per colony administered in 3 applications of sugar syrup or 3 dustings at 4- to 5-day intervals. Dust should be applied on the outer parts or ends of the frames.

K. Route of Administration

Oral

L. Species/Class

Honey bees

M. Indication

For control of American Foulbrood caused by *Paenibacillus larvae*.

N. Effect of Supplement

This supplement provides for the establishment of a tolerance of 750 ppb for the sum of tetracycline residues 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 008-622 dated July 9, 2000, contains dosage characterization information for the use of 200 mg oxytetracycline HCl per colony of honey bees in three applications at 4- to 5-day intervals.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 008-622 dated July 9, 2000, contains a summary of information that demonstrate effectiveness of the drug for the use of 200 mg oxytetracycline HCl per colony of honey bees in three applications at 4- to 5-day intervals.

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 008-622 dated July 9, 2000, contains a summary of target animal safety information for the use of 200 mg oxytetracycline HCl per colony of honey bees in three applications at 4- to 5-day intervals.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

No information or data were required to address microbial food safety (antimicrobial resistance) for this supplemental application where the only action was assignment and publication of an official tolerance value for residues of oxytetracycline in honey.

B. Toxicology

Reassessment of the acceptable daily intake (ADI) of 25 µg/kg of body weight per day for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) as codified under 21 CFR 556.500 was not needed for this supplemental approval. This ADI is based on a review of all tetracyclines (NADA 113-232, dated May 31, 1996).

C. Safe Concentrations for Total Residues in Edible Tissues

Reassessment of the safe concentrations for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) for muscle, liver, kidney, and fat was not needed for this supplemental approval. The safe concentrations of total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) in individual edible tissues are 2 parts per million (ppm) for muscle, 6 ppm for liver, 12 ppm for kidney, and 12 ppm for fat.

The safe concentration for total oxytetracycline residues in honey is calculated as follows, using 1% of the ADI and a food consumption value of 20 g for honey:

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

$$\text{Safe Concentration} = \frac{1\% \times 25 \text{ } \mu\text{g/kg body weight/day} \times 60 \text{ kg}}{20 \text{ g/day}} = 0.75 \text{ } \mu\text{g/g} = 0.75 \text{ ppm}$$

Therefore, the safe concentration for total residues of oxytetracycline is 0.75 ppm or 750 parts per billion (ppb) for honey.

D. Residue Chemistry

1. Summary of Residue Chemistry Studies

CVM did not require residue chemistry studies for this supplemental approval. CVM conducted an exposure assessment to assign a tolerance for residues of oxytetracycline in honey.

The ADI for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) is 25 µg/kg of body weight per day. This results in an acceptable daily consumption of 1500 µg of total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) per person.

ADI = 25 µg/kg body weight × 60 kg body weight/person = 1500 µg per person

The ADI for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) is partitioned 40% for tissues and 60% for milk. However, only 30% of the ADI was used to assign a tolerance for oxytetracycline in milk (FOI Summary for the supplemental approval of NADA 113-232, dated July 21, 1998), leaving 30% (450 µg/person/day) of the ADI unutilized. It is consistent with public health to assign a tolerance in honey that utilizes part of the unutilized portion of the ADI.

A tolerance of 750 ppb (750 µg/kg) for residues of oxytetracycline results in an exposure that represents 1% of the ADI for total residues of oxytetracycline. This ensures that the ADI for total residues of oxytetracycline is not exceeded.

Exposure, µg = 750 µg residues oxytetracycline/kg honey × 0.02 kg honey/person/day

Exposure, µg = 15 µg/person/day

Exposure, % ADI = 15 µg/person/day ÷ 1500 µg/person/day × 100%

Exposure, % ADI = 1% of the ADI

Incurred residue concentrations were obtained from published literature (*Apidologie* **12(2)**: 133 - 136 (1981)). Table IV.1 reports the concentration of residues of oxytetracycline in honey following various dosing schemes. The analytical method also detected natural compounds in honey that exhibit bactericidal properties. Therefore, during the exposure assessment, CVM subtracted a background value of 550 ppb from the analytical method results to obtain the results reported in Table IV.1.

Table IV.1. Concentration of residues of oxytetracycline (OTC) in honey reported in *Apidologie* **12(2)**: 133 - 136 (1981)

Application Type	Time After Last Treatment	Colony 1	Colony 2	Colony 3
200 mg OTC extender patty (one application)	39 Days	Not detected	Not detected	Not detected
400 mg OTC extender patty (one application)	39 Days	Not detected	Not detected	150 ppb
200 mg OTC in powdered sugar (three applications)	25 Days	650 ppb	3050 ppb	Not detected
200 mg OTC in sugar syrup (one application)	26 Days	Not detected	Not detected	Not detected
Control	Not Applicable	Not detected	Not detected	Not detected

Based on the underutilization of the ADI in milk and the reported concentrations of oxytetracycline residues in honey, a tolerance of 750 ppb for residues of oxytetracycline is consistent with public health. Because the analytical method for detection of residues of oxytetracycline is a microbiological assay, the tolerance of 750 ppb is for the sum of tetracycline residues in honey.

2. Target Tissue and Marker Residue

The target tissue is honey, and the marker residue is the sum of tetracycline residues.

3. Tolerance

A tolerance of 750 ppb is established for the sum of tetracycline residues in honey.

4. Withdrawal period

Treatment should be removed at least 6 weeks prior to main honey flow (21 CFR 558.450).

E. Analytical Method for Residues

1. Description of Analytical Method

The analytical method for detection of oxytetracycline residues is a microbiological test using *Bacillus cereus* var. *mycoides* (ATCC 11778).

2. Availability of the Method

The analytical method for analysis of residues of oxytetracycline is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. 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 Terramycin[®], Terramycin[®] Soluble Powder Concentrate, and Terramycin-343[®]:

FOR ANIMAL USE ONLY. KEEP OUT OF REACH OF CHILDREN. Not for Human Use. Use Only As Directed.

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 Terramycin[®], Terramycin[®] Soluble Powder Concentrate, and Terramycin-343[®], when used according to the label, are safe and effective for control of American Foulbrood caused by *Paenibacillus larvae*. Additionally, data demonstrate that residues in food products derived from species treated with Terramycin[®], Terramycin[®] Soluble Powder Concentrate, and Terramycin-343[®] 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

Terramycin[®], Terramycin[®] Soluble Powder Concentrate, and Terramycin-343[®], as approved in our approval letter, do 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.