

Date of Approval: December 20, 2019

**FREEDOM OF INFORMATION SUMMARY**  
**SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION**

NADA 111-636

LINCOMIX<sup>®</sup> Soluble Powder

lincomycin hydrochloride

Honey bees

This supplement provides for the establishment of a tolerance of 750 parts per billion (ppb) for residues of lincomycin 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 .....	4
A. Microbial Food Safety .....	4
B. Toxicology .....	4
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 .....	7
A. Marketing Status.....	7
B. Exclusivity.....	7
C. Supplemental Applications .....	8
D. Patent Information.....	8

**I. GENERAL INFORMATION**

**A. File Number**

NADA 111-636

**B. Sponsor**

Zoetis Inc.  
333 Portage St.  
Kalamazoo, MI 49007

Drug Labeler Code: 054771

**C. Proprietary Name**

LINCOMIX® Soluble Powder

**D. Drug Product Established Name**

Lincomycin hydrochloride

**E. Pharmacological Category**

Antimicrobial

**F. Dosage Form**

Powder for solution

**G. Amount of Active Ingredient**

0.4 grams lincomycin hydrochloride equivalent to lincomycin per gram of powder  
(188.4 g/lb)

**H. How Supplied**

1.41 oz (40 grams) packet  
2.82 oz (80 grams) packet  
5.64 oz (160 grams) bottle  
16.92 oz (480 grams) bottle

**I. Dispensing Status**

Rx

**J. Dosage Regimen**

100 mg lincomycin per hive mixed with 20 g confectioners'/powdered sugar  
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**

LINCOMIX® Soluble Powder is indicated for the control of American foulbrood (*Paenibacillus larvae*) in honey bees

**N. Effect of Supplement**

This supplement provides for the establishment of a tolerance of 750 ppb for residues of lincomycin 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 111-636 dated March 27, 2012, contains dosage characterization information for the use of 100 mg lincomycin per hive weekly for 3 weeks in honey bees.

**B. Substantial Evidence**

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 111-636 dated March 27, 2012, contains a summary of studies that demonstrate effectiveness of the drug for the use of 100 mg lincomycin per hive weekly for 3 weeks in honey bees.

**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 111-636 dated March 27, 2012, contains a summary of target animal safety studies for the use of 100 mg lincomycin per hive weekly for 3 weeks in honey bees.

**IV. HUMAN FOOD SAFETY**

**A. Microbial Food Safety**

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

**B. Toxicology**

Reassessment of the acceptable daily intake (ADI) of 25 µg/kg bw/day for total residues of lincomycin as codified under 21 CFR 556.360 was not needed for this supplemental approval. The FOI Summaries for the supplemental approvals of NADA 097-505, dated May 1, 1990, and August 25, 1998, and NADA 111-636,

dated January 23, 1990, and August 25, 1998, contain a summary of all toxicology studies and information.

**C. Safe Concentrations for Total Residues in Edible Tissues**

Reassessment of the safe concentrations for total residues of lincomycin for muscle, liver, kidney, and fat was not needed for this approval. The safe concentrations of total residues of lincomycin in individual edible tissues of swine are 5 ppm for muscle, 15 ppm for liver, 30 ppm for kidney, and 30 ppm for fat.

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

$$\begin{aligned} \text{Safe Concentration} &= \frac{1\% \text{ ADI} \times \text{Human Body Weight}}{\text{Food Consumption Value}} \\ &= \frac{1\% \times 25 \mu\text{g/kg bw/day} \times 60 \text{ kg}}{20 \text{ g/day}} = 0.75 \mu\text{g/g} = 0.75 \text{ ppm} \end{aligned}$$

**D. Residue Chemistry**

1. Summary of Residue Chemistry Study

The residue chemistry study reported in the FOI Summary for the supplemental approval of NADA 111-636 dated March 27, 2012, was used to support this supplemental approval to establish a tolerance for residues of lincomycin in honey. Residues of lincomycin in honey seen in the residue chemistry study under field conditions are presented in Tables 1 and 2.

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

Treatment	7 days after final treatment	14 days after final treatment	20 days after final treatment
200 mg*	1.22 (0.73, 2.12)	0.65 (0.40, 1.09)	0.41 (0.26, 0.67)
1000 mg*	13.94 (7.15, 29.80)	2.41 (1.39, 4.31)	1.57 (0.92, 2.73)
0 mg (control)	0.39 (0.25, 0.64)	0.15 (0.10, 0.23)	0.12 (0.08, 0.19)

\*Doses are designated 1X and 5X for the field study report but represent 2X and 10X relative to the approved label dose.

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

Treatment	0 day (on treatment)	7 days after final treatment	14 days after final treatment	20 days after final treatment
200 mg*	4.37 (2.40, 8.14)	0.15 (0.10, 0.24)	0.29 (0.18, 0.47)	0.38 (0.24, 0.62)
1000 mg*	6.91 (3.71, 13.48)	0.48 (0.30, 0.80)	1.29 (0.76, 2.24)	1.51 (0.89, 2.63)
0 mg (control)	0.25 (0.16, 0.40)	0.15 (0.10, 0.24)	0.16 (0.10, 0.25)	0.26 (0.17, 0.42)

\*Doses are designated 1X and 5X for the field study report but represent 2X and 10X relative to the approved label dose.

Based on the incurred residues seen in the field study at 20 days post-treatment for the 200 mg dosing, we assign a tolerance of 750 µg lincomycin/kg honey (0.75 mg lincomycin/kg). The tolerance assignment is consistent with the upper 95% confidence limit residue value and represents 1% of the ADI, adjusted for the consumption value of honey, 20 g/person/day:

$$\begin{aligned} \text{ADI} &= 25 \mu\text{g/kg body weight} \times 60 \text{ kg/person} = 1500 \mu\text{g/person} \\ 1\% \text{ ADI} &= 15 \mu\text{g/person} \\ \text{Consumption value} &= 0.02 \text{ kg honey/person} \\ \text{Exposure} &= 15 \mu\text{g lincomycin/person} \div 0.02 \text{ kg honey/person} = 750 \mu\text{g/kg} \end{aligned}$$

Because the ADI is a microbiological ADI, the tolerance is equivalent to the safe concentration for total microbiological residues. Residues in the field study were determined using a microbiological assay.

## 2. Target Tissue and Marker Residue

The target tissue is honey. A marker residue is not identified because the regulatory method measures microbiological activity of lincomycin rather than a specific compound.

## 3. Tolerance

A tolerance of 750 ppb is established for residues of lincomycin in honey.

## 4. Withdrawal Period

Complete treatments at least four weeks before main honey flow.

## **E. Analytical Method for Residues**

### 1. Description of Analytical Method

The analytical method for the detection of residues of lincomycin 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). This method is found in "Diagnosis of Honeybee Diseases," Shimanuki, H, and Knox, D. A. 2000. US Department of Agriculture, Agricultural Handbook No. AH-690.

### 2. Availability of the Method

A copy of the method 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 LINCOMIX® Soluble Powder:

WARNING: 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 (FD&C Act) and 21 CFR part 514. The data demonstrate that LINCOMIX® Soluble Powder, when used according to the label, is safe and effective for control of American foulbrood (*Paenibacillus larvae*) in honey bees. Additionally, data demonstrate that residues in food products derived from species treated with LINCOMIX® Soluble Powder 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**

LINCOMIX® Soluble Powder, as approved in our approval letter, does not qualify for a 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.