Approval Date: December 23, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-929

B. Sponsor

Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

C. Proprietary Name

Micotil® 300 Injection

D. Established Name

tilmicosin phosphate

E. Dosage Form

Micotil 300 INJECTION is available in 50 mL, 100 mL, and 250 mL multidose amber glass bottles.

F. Dosage Regimen

Administer a single subcutaneous dose of 10 mg/kg of body weight (1 mL/30 kg or 1.5 mL/100 lb.). Do not inject more than 15 mL per injection site.

G. Route of Administration

MICOTIL 300 INJECTION is supplied ready to use for subcutaneous injection in cattle. Injection under the skin, behind the shoulders and over the ribs is suggested.

H. Indication

“For the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*. For the control of respiratory disease in cattle at high risk of developing BRD associated with *P. haemolytica*.”

I. Effect of Supplement

Deletes the following statements from the label: "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal."

II. EFFECTIVENESS

No new efficacy data were required for the approval of this supplement. See original FOI summary dated March 24, 1992.

III. ANIMAL SAFETY

No new animal safety data were required for approval of this supplement. See original FOI summary dated March 24, 1992.

IV. HUMAN FOOD SAFETY

A. Toxicity Studies

No new toxicity studies were required for this approval. See original FOI summary dated March 24, 1992.

B. Safe Concentrations of Total Residues

The toxicity studies submitted with the original NADA 140-929 were used to establish the following safe concentrations for tilmicosin total residues in tissues of cattle.

Tissue	**Safe Concentration (ppm)**
Muscle	4.8
Liver	9.6
Kidney	14.4
Fat	19.2

C. Target Tissue, Marker Residue, and Tolerance (Rm)

The total residue and metabolism data submitted with the original NADA 140-929 established liver as the target tissue and parent tilmicosin as the marker residue for tilmicosin in cattle. Those data also established 1.2 ppm as the tolerance for parent tilmicosin in cattle liver (21 CFR 556.735).

D. Marker Residue Depletion (Withdrawal) Study

A residue depletion study using the marketed Micotil injectable product was conducted in pre-ruminating calves in order to confirm the the 28-day withdrawal time approved for beef cattle is valid withdrawal time for pre-ruminating calves.

1. Study T5C619603: Tilmicosin Tissue Residue Decline Study in Calves Less Than One Month of Age.

2. Investigators:

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   Animal Science Product Development
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3. Objectives: This study was conducted to determine the concentration of tilmicosin in liver tissue of pre-ruminating calves less than one month of age at various withdrawal times after a single subcutaneous injection of 300 mg/mL tilmicosin (Micotil 300 Injection) at 10 mg/kg body weight, thus defining the tissue residue decline rate.

4. Test Article: The test article was Micotil 300 Injection (Lot 9MM74M) obtained from the commercial production source.

5. Design: Twenty-five Holstein or Holstein/Angus Cross calves, three to five days of age, were each injected once with Micotil at 10 mg/kg body weight. Five calves, three males and two females, were killed at each of the following times after treatment: 14, 21, 28, 35, and 42 days. Calves were fed an unmedicated commercial calf milk replacer twice a day throughout the study.

6. Assays: Liver tissue collected from each animal at death was assayed by high performance liquid chromatography (HPLC) for tilmicosin content using an official method with a limit of quantitation of 0.05 ppm. Liver was assayed because it is the target tissue and tilmicosin was measured because it is the marker residue (NADA 140-929, 21 CFR 556.735).

7. Results: Liver residue concentrations are summarized in Table 6.1.

Table 6.1. Tilmicosin concentration in the liver of pre-ruminating calves at various times after a single subcutaneous injection of 10 mg tilmicosin/kg.

Withdrawal (days)	Number of Animals	Mean Tilmicosin Concentration in Liver (µg/g)
14	5	1.18 (± 1.01)
21	5	0.21 (± 0.11)
28	5	1.12 (± 0.05)
35	5	0.09 (± 0.03)
42	5	0.06 (± 0.01)

Data were analyzed using statistical techniques as suggested in Section IV., Guideline for Establishing A Safe Concentration, *In: General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals*, revised July 1994. Withdrawal times and tolerance limit values were calculated based on a statistical tolerance limit procedure (Owen) using the 99th percentile of the population and the 95% confidence interval. The time to reach a liver tilmicosin concentration of 1.2 ppm was calculated to

be 28 days.

E. Confirmation of the Withdrawal Time

The tilmicosin residue data in liver from study T5C619603 were analyzed using the agency's statistical tolerance limit method (99% tolerance limit with a 95% confidence interval). It was concluded from those calculations that, if Micotil is used at the current label dose in pre-ruminating calves, followed by the label withdrawal of 28 days before slaughter, residues of tilmicosin will not exceed the established marker residue tolerance in liver.

F. Regulatory Method

The official regulatory determinative and confirmatory tissue assay procedures are summarized in the FOI Summary for the original NADA 140-929.

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data from the residue depletion study with a single subcutaneous injection of tilmicosin (10 mg/kg body weight) in pre-ruminating calves demonstrate that the current 28-day withdrawal time assigned with the cattle approval is an adequate withdrawal time for calves being raised for veal. The residue data support the removal of Micotil label warning statement against the use of this drug in calves to be processed for veal. However, there are no other data submitted to demonstrate its safety and effectiveness in veal calves. Therefore, this drug is not approved for use in veal calves and, as such, should not be promoted for use in this class of animals.Under the Center's supplemental approval policy [21 CFR 514.106(b)(2)(ix)], this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety and effectiveness of this new animal drug and, therefore, did not require a reevaluation of the human food or target animal safety data in the parent application.

The product remains a prescription drug for safe and effective use by a veterinarian in cattle for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*, and for the control of respiratory disease in cattle at high risk of developing BRD associated with *P. haemolytica*.

The agency has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Tilmicosin is under patent number U.S. 4,820,695 expiring April 11, 2006.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.