Approval Date: December 30, 1996

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

D. Established Name

tilmicosin injection USP

E. Dosage Form

MICOTIL® 300 injectable is available in 50-, 100-, and 250-mL bottles of ready-to-use solution containing 300 mg tilmicosin phosphate per milliliter.

F. Dosage Regimen

A single subcutaneous injection of 10 mg tilmicosin per kilogram of body weight (1 mL per 30 kg or 1 1/2 mL per 100 lb of body weight).

G. Route of Administration

MICOTIL® 300 is to be administered by subcutaneous injection to cattle

H. Indication

Provides for the use of tilmicosin phosphate (Micotil® 300) in cattle for a new therapeutic claim.

I. Effect of Supplement

Provides for the use of tilmicosin phosphate (Micotil® 300) in cattle for a new therapeutic claim.

II. EFFECTIVENESS

An original new animal drug application (NADA) for MICOTIL® 300 (NADA 140-929) was approved March 24, 1992 (57 FR 12711, April 13, 1992). MICOTIL® 300 is approved for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica* by a single subcutaneous injection of 10 mg tilmicosin per kilogram of body weight. Dose-range-finding studies and field trials conducted for the original NADA are summarized in the Freedom of Information (FOI) Summary.

For the purposes of this supplemental approval, a field trial in high-risk feedlot calves indicated that the previously-approved dose of tilmicosin (10 mg/kg of body weight) was effective for the control of respiratory disease in cattle at high risk of developing BRD, when those cattle were treated early, before all demonstrated signs of clinical disease. The incidence of clinical disease (morbidity) was significantly reduced by treatment with MICOTIL® 300 when the conditions were such that the feedlot veterinarian expected a high percentage of the calves to become clinically ill with BRD. The incidence of death associated with BRD (mortality) was also reduced, but was a secondary measure because intervention in the form of different treatment regimens was administered after determining illness.

A. Pivotal Field Trial: T5C489405

1. Type of Study: A clinical field study was conducted using MICOTIL® 300 in feedlot calves which were judged to be at high risk of becoming clinically ill (through natural means) with BRD.

2. Investigator

   Dr. Abe Turgeon
   Bos Technica Research Center
   Dumas, Texas

3. General Design

   a. Purpose: The objective of this study was to determine the effect of tilmicosin on the incidence of morbidity and mortality due to BRD in high risk cattle when used in temperature-based and early treatment programs during the first 28 days on feed.

   b. Animals: 1058 cattle with an initial average body weight of 555 lb were purchased from livestock auction facilities in Arkansas and Texas and transported to Dumas, Texas. Cattle were of mixed breed, type and origin, and were mixed steers and bulls. All animals in one treatment group received a single dose of MICOTIL® 300 at processing, while all animals in a second treatment group received a single dose of MICOTIL® 300 only if their body temperature equaled or exceeded 104.0°F.

   c. Controls: Control animals were randomly selected from the same group of cattle used for treatment, but received no antibiotic treatment at processing.

   d. Diagnosis: The trial facility, cattle, and conditions for the trial were selected to insure that the cattle would be highly likely to develop BRD shortly after arrival. Cattle actually exhibiting signs of BRD or other

disease at the first processing were excluded from the trial, so that only cattle not yet showing signs of BRD were used. Morbidity was based on a clinical impression resulting from observing attitude, respiration rate, dyspnea, gauntness, and nasal and/or ocular discharge. When animals were pulled for treatment, the rectal body temperature was recorded.

e. Dosage Form: MICOTIL® 300 injectable solution, 300 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Dose: 10 mg tilmicosin/kg body weight.

h. Test Duration: The test spanned 28 days.

i. Pertinent Variables Measured: The principal criteria of efficacy was morbidity.

4. Results

Table 4.1 summarizes by treatment group, the effects of tilmicosin on morbidity and mortality when used in temperature-based and early treatment programs. When compared to controls, use of tilmicosin in the early treatment program resulted in a morbidity of 29.9% compared to 53.1% in the control group ($p = 0.02$, two-sided) during the 28-day observation period. Groups given early treatment with tilmicosin exhibited lower morbidity than the temperature-based groups which had a morbidity of 40.7% but were not significantly different ($p = 0.17$, two-sided). When mortality rates were observed, early treatment with tilmicosin reduced mortality from 1.97% to 0.57% when compared with controls. Mortality in the early treatment program was also reduced when compared to mortality in the temperature-based program.

Table 4.1. Effect of early treatment with tilmicosin (10 mg/kg) on the incidence of clinical illness (morbidity) and death (mortality) due to bovine respiratory disease when used in temperature-based or early treatment programs

Treatment program	**Percent morbidity**	**Percent morbidity**
Control	53.1(a) (189/356)	1.97 (7/356)
Temperature-based	40.7(a,b) (143/351)	0.85 (3/351)
Early treatment	29.9(b) (105/351)	0.57 (2/351)

a,b Mean with different letters are significantly different, $p < .05$.

5. Statistical Analysis: The data from this field trial was analyzed using a mixed models procedure. The REML estimation procedure was used. Prior to the analysis, the pen proportions for morbidity were re-expressed with the arcsine transformation typically used to stabilize the variance of proportions. A pen sample size weighted analysis was performed to adjust for the varying number of animals per pen.

6. Conclusions: These data demonstrate that MICOTIL® 300, as a single subcutaneous injection (10mg/kg body weight), is effective for the control of

respiratory disease in cattle at high risk of developing BRD associated with *P. haemolytica*.

7. Adverse Reactions: No adverse reactions were noted.

B. Corroborative Studies

The following published articles provide additional evidence on the effectiveness of tilmicosin treatment on newly-arrived feedlot calves.

1. Galyean, M.L., S.A. Gunter and K.J. Malcom-Callis. 1995. Effects of arrival medication with tilmicosin phosphate on health and performance of newly received beef cattle. *Journal of Animal Science*. **73**:1219-1226.

   Abstract: Three trials were conducted to evaluate the use of tilmicosin phosphate (Micotil®) as a prophylactic medication for newly received, stressed beef cattle. In Trial 1, 57 beef calves (average initial BW = 170 kg) were shipped to the research feedlot from Tennessee and either given no antibiotic at processing or treated with Micotil at 10 mg of tilmicosin phosphate/kg of BW. During a 28-d receiving period, treatment at processing with Micotil did not affect daily gain ($P < .17$) or DMI ($P < .22$) compared to control calves. Prophylactic treatment with Micotil decreased ($P < .01$) the percentage of calves treated for symptoms of bovine respiratory disease from 46.4 to 0%. In Trial 2, 117 calves (average initial BW = 191 kg) were shipped from Tennessee and allotted randomly to the same two treatments as in Trial 1. All calves grazed a 24-ha pasture of irrigated winter wheat during the 29-d receiving period. Treatment of calves with Micotil at the time of arrival processing did not affect ($P > .50$) daily gain during the trial; however, as in Trial 1, mass treatment with Micotil decreased ($P < .01$) the percentage of calves treated for respiratory disease from 32.8% to 12.1%. In Trial 3, two truckloads of beef calves (183 total; average initial BW = 232 kg) shipped from Tennessee were allotted randomly to the same two treatments used in Trials 1 and 2 or to a third treatment that consisted of administration of Micotil at arrival processing if the rectal temperature of the calf was > or = 39.7°C. Treatment at arrival processing with Micotil, whether on a mass basis or based on rectal temperature, increased daily gain during initial 28-d receiving period ($P < .01$) and a subsequent 29-d feeding period ($P < .07$). Dry matter intake was greater ($P < .05$) and feed:gain ratio was lower ($P < .03$) for both groups of Micotil-treated calves than for control calves for the overall 56-d trial. Both mass treatment (11.9%) and rectal temperature-based treatment (21.9%) of calves with Micotil decreased ($P < .01$) the percentage of calves treated for respiratory disease compared with controls (43.6%). Micotil seems to be a highly effective prophylactic medication for newly received beef cattle that have been subjected to shipping stress. Application of Micotil based on rectal temperature of calves at the time of processing was as effective as mass treatment.

2. Morck, D.W., J.K. Merrill, B.E. Thorlakson, M.E. Olson, L.V. Tonkinson and J.W. Costerton. 1993. Prophylactic efficacy of tilmicosin for bovine respiratory tract disease. J*ournal American Veterinary Medical Association*. **202**:273-277.

Abstract: The prophylactic administration of injectable tilmicosin for pneumonia in weaned beef calves was investigated in 1,806 animals. Comparisons were made among calves receiving an "on-arrival" injection of tilmicosin, calves receiving a single injection of long-acting oxytetracycline, and calves receiving no prophylaxis. Morbidity and mortality attributable to pneumonia, morbidity and mortality attributable to all causes, and case fatality were significantly lower in the group of calves that received tilmicosin, compared with calves that received long-acting oxytetracycline and calves that received no prophylactic antibiotic. Mean time to initial pneumonia treatment was significantly extended in calves that received prophylaxis, compared with those that received no antibiotic on arrival at the feedlot. Calves that received tilmicosin gained significantly more weight than calves that received oxytetracycline. Calves that were not treated for pneumonia during the trial period gained significantly more weight than did those calves that were treated for pneumonia regardless of experimental group. The majority of mortalities were attributable to fibrinous pneumonia (31/34). Important bacterial isolates (*Pasteurella spp, Haemophilus somnus, Actinomyces pyogenes*) obtained at necropsy did not have resistance to tilmicosin in association with administration of tilmicosin as prophylaxis for pneumonia. However, bacterial resistance to trimethoprim/sulfonamide and to oxytetracycline were commonly found in these postmortem isolates.

3. Schumann, F.J., E.D. Janzen and J.J. McKinnon. 1990. Prophylactic tilmicosin medication of feedlot calves at arrival. *Canadian Veterinary Journal*. **31**:285-288.

Abstract: The parenteral administration of the antibiotic tilmicosin given on arrival at a feedlot was evaluated in a group of 304 steer calves. These calves were allotted to 24 pens so that there were 12 replicates of both control and medicated groups. The treatment rate was reduced significantly during the first five days ($p < 0.05$) and during the first month ($p < 0.01$) of the feeding period in the medicated group. The average days from arrival until first treatment for respiratory disease was increased to 21 days in the medicated group compared to 9 days ($p < 0.01$) for the controls. The medicated group had improved average daily gain ($p < 0.01$) and feed efficiency ($p < 0.01$) over the trial period when compared to the nonmedicated animals.

4. Schumann, F.J., E.D. Janzen and J.J. McKinnon. 1991. Prophylactic medication of feedlot calves with tilmicosin. *Veterinary Record*. **128**:178-280.

Abstract: The parenteral administration to calves of the antibiotic tilmicosin either on arrival at a feedlot or 72 hours later was

evaluated in a group of 308 steer calves. The calves were allotted to 24 pens so that there were eight replicates of the two medicated groups and eight replicates of the control group. The need for veterinary treatment was reduced significantly ($P < 0.05$) during the first month of the feeding period in the two medicated groups. The medicated groups had an improved average daily weight gain ($P < 0.01$) over the trial period compared with the non-medicated animals. This improved average daily gain by the medicated groups was not reduced when animals with respiratory disease were excluded from the calculations. The medicated groups also had an improved feed conversion efficiency ($P < 0.01$) over the first 60 days of the feeding period compared with the non-medicated animals.

III. ANIMAL SAFETY

This supplemental approval for a new indication does not change the dose of tilmicosin, the frequency or route of administration. Accordingly, no additional studies were considered for animal safety. See the Freedom of Information (FOI) Summary for the approval of the original application for MICOTIL® 300 (NADA 140-929), approved March 24, 1992.

IV. HUMAN FOOD SAFETY

This supplemental approval for a new indication does not change the dose of tilmicosin, the frequency or route of administration. Accordingly, no additional studies were considered for human food safety. See the Freedom of Information (FOI) Summary for the approval of the original application for MICOTIL® 300 (NADA 140-929), approved March 24, 1992.

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that MICOTIL® 300 (tilmicosin phosphate), when administered as a single subcutaneous injection to cattle, is safe and effective for the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica*.

Under the Center's supplemental approval policy [21 CFR 514.106(b)(2)(v) and (vii)], this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or 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 the control of respiratory disease in cattle at high risk of developing BRD associated with *P. haemolytica.*

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding contained in an environmental assessment may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, Maryland 20857.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the supplement and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new claim, control of respiratory disease in cattle at high risk of developing BRD associated with *P. haemolytica*, for which the supplemental application was approved.

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.