FREEDOM OF INFORMATION SUMMARY
MONENSIN FOR COCCIDIOSIS PREVENTION IN GOATS

I. General Information:

A. NADA Number: 95-735

B. Sponsor: Elanco Products Company
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

C. Generic Name: monensin

D. Trade Name: RUMENSIN®- (Monensin Sodium, Elanco Products Company)

E. Marketing Status: OTC

F. Effect of Supplement: This supplement provides for an expanded use of monensin in a new animal species.

II. Indications For Use:

For the prevention of coccidiosis caused by *Eimeria crandallis*, *E. christenseni* and *E. ninakohlyakimovae* in goats maintained in confinement.

III. Dosage Form:

Type A Medicated Article for inclusion in Type C finished feeds.
Recommended Dosage: Feed continuously as sole ration at the rate of 20 g monensin per ton of complete feed.

IV. Effectiveness

Refer to PMF 5055, 51 FR 45555, December 19, 1986.

V. Animal Safety

Refer to PMF 5055 for the pivotal study.

A. Ancillary Safety Study
EVALUATION OF THE SAFETY OF MONENSIN WITH ANGORA KID GOATS

Location: Texas Agricultural Research Center, San Angelo, Texas

Investigator: Millard C. Calhoun, Ph.D.
Texas A&M University
San Angelo, Texas

Summary: The objective of the study was to evaluate the safety of monensin fed to Angora kid goats at levels 1, 2, 3, 4, and 5 times the recommended level of 20 g/ton for a period of 28 days.

Thirty 4-month old Angora kid goats of mixed sex were used in this study. After an acclimation period, twenty goats were assigned at random to each of five dietary monensin levels (20, 40, 60, 80 and 100 g monensin/ton of feed). The feeds were fed for a 28-day period.

A summary of live weights, gains, feed intakes and fecal oocyst numbers of Angora kid goats fed the diets containing different levels of monensin for 28 days is presented below. No data are included in this summary for two goats that died due to coccidial infection. There was a linear decrease in live weight gains ($P<0.10$) and feed intake ($P<0.01$) as the level of monensin in the diet increased. Initially, fecal oocyst numbers were high and variable. However, all monensin levels resulted in a marked reduction in fecal oocysts, and 20 g/ton was as effective as the higher levels.

There were no apparent changes related to the monensin treatments in any of the measurements of hematocrit and serum constituents. An increase in hematocrit values during the experiment probably reflected the beneficial effects of monensin in decreasing coccidial infections and was uniform across all treatments. One goat receiving 60 g of monensin/ton ate considerably less feed during the experiment than other goats receiving the same treatment. This goat consumed almost no feed during the second and third weeks of the experiment and had elevated serum levels of lactate dehydrogenase and glutamic-oxalacetic transaminase. Fecal coccidial oocyst numbers for this goat were 101,000/g initially and 31,700/g after 28 days, indicating that a continuing coccidial infection and reduced feed intake may have been contributing factors to the increased serum levels of lactate dehydrogenase and glutamic-oxalacetic transaminase observed at 28 days. Since similar increases in the levels of these serum enzymes were not observed in any of the goats receiving either the 80 or 100 g/ton levels of monensin, these increases are probably not related to monensin. One other goat on the 60 g of monensin/ ton level had elevated initial and final values for serum alkaline phosphatase. These elevated values are also considered to be unrelated to monensin treatments.

Live Weights, Gains, Feed Intakes, and Fecal Oocyst Numbers of Angora Kid Goats Fed Diets Containing Different Levels of Monensin for 28 Days

Item	20 g/ton Monensin	40 g/ton Monensin	60 g/ton Monensin	80 g/ton Monensin	100 g/ton Monensin	SD[a]	CV[b]
Goats Started, no.	4	4	4	4	4	-	-
Goats Dies, no.	0	0	1	1	0	-	-
Initial Live Weight, kg	16.6	16.7	15.9	15.1	15.7	1.4	8.6
Live Weight Gain, kg[c]	4.2	2.8	1.5	1.4	0.3	2.1	99.6
Feed Intake, kg[d]	29.4	21.3	17.8	14.0	12.6	6.6	34.3
Oocysts, no./g feces x 10^3 Initial	74.1	169.3	61.3	37.8	85.7	129.0	143.9
Final	1.5	0.4	11.3	0.1	2.5	7.4	254.8

[a] Standard deviation
[b] Coefficient of variation
[c] Linear effect of monensin ($P<0.10$)
[d] Linear effect of monensin (<0.01)

VI. Human Safety

A. Toxicity Tests:
The following toxicity tests were considered in establishing the tolerance for monensin:

1. Chronic Mouse Study

a. Title: "A Chronic Toxicity- Oncogenicity Study in $B6C3F_1$ Mice Maintained for Two Years on Diets Containing Mycelial Monensin Sodium"

b. Report Number: Studies M00281 and M00381

c. Starting Date: January 13, 1981

d. Termination Date: January 28, 1983

e. Names and addresses of investigators who did the study:
Dr. L. C. Howard and Dr. M. N. Novilla
Lilly Research Laboratories
Greenfield, Indiana 46140

f. Name and address of laboratory where study was done:
Toxicology Division
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

g. Study Description and Conclusions:
Groups of 60 male and 60 female B6C3F_1 mice, started on test at five to six weeks of age, were maintained for two years on diets containing 0.0, 0.001, 0.0025, 0.0075 and 0.015% (0, 10, 25, 75 and 150 ppm) of monensin sodium activity . These concentrations provided an estimated time-weighted average daily dose of 0.0, 1.2, 3.1, 10.2 and 22.6 mg/kg for males and 0.0, 1.4, 3.5 , 11.7 and 25.6 mg/kg for females.

Survival was not adversely affected by monensin treatment. At 24 months, 88, 85, 80, 85 and 90% of the males and 78, 81, 85, 78 and 95% of the females were alive in the 0.0, 0.001, 0.0025, 0.0075 and 0.015% groups, respectively. Observations for physical or behavioral signs of toxicity did not reveal any effects related to monensin treatment. Primary drug-related effects were observed in decreased weight and weight gain at the three highest doses for both males and females. Depressed organ weights were observed for both sexes at the two highest doses of monensin for liver, kidney, and heart and spleen at the highest doses. The effects on organ weight parameters were probably associated with the effects on body weight gain. Dose-related changes resulted in decreased leukocyte counts for the three highest male treatment groups. There were minimal changes in differential leukocyte counts and erythrocyte parameters. The observed changes in the latter were primarily in the highest female treatment group. Clinical chemistry changes were confined to the highest treatment group and primarily to the male group.

A variety of inflammatory, degenerative and neoplastic lesions was found, the types and incidence of which were characteristic of aging mice. There was no gross or microscopic evidence of carcinogenicity or chronic toxicity attributable to monensin administration.

In conclusion, the dietary administration of monensin to mice for two years at levels as high as 0.015% did not produce a carcinogenic or oncogenic effect. Based upon the effects on body weight and leukocyte counts, the no-effect level is 0.001%, the lowest treatment group. Based on the estimated overall mean daily intake of monensin, the no-observed-effect level is 1.27 mg/kg/day for monensin (mycelial).

2. Chronic Rat Study

a. Title: "A Chronic Toxicity – Oncogenicity Study in Wistar Rats Maintained for Two Years on Diets Containing Mycelial Monensin Sodium"

b. Report Number: Studies R06378 and R06478

c. Starting Date: June 27, 1978

d. Termination Date: July 10, 1980

e. Names and addresses of investigators who did the study:
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Lilly Research Laboratories
Greenfield, Indiana 46140

f. Name and address of laboratory where study was done:
Toxicology Division
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

g. Study Description and Conclusions: Groups of 100 male and 100 female Wistar rats, six to eight weeks of age and derived from parents given diets containing monensin sodium, were maintained for two years on diets containing 0, 0.0033, 0.005 and 0.008% (0, 33, 50 and 80 ppm) monensin sodium activity as mycelial monensin sodium. These concentrations provided a time weighted average daily dose of 1.40, 2.18 and 3.60 mg monensin sodium activity/kg for males and 1.72, 2.86 and 5.02 mg monensin sodium activity/kg for females.

At the beginning of the study, body weights were decreased in relationship to dose. This was statistically significant for males from the 0.008% group and for females from the 0.005% and 0.008% groups and was the result of dose-related decreases in weight gain for the parent generation, for the pups during postpartum development, and for the weaned animals until assignment to studies R06378 and R06478. Statistically significant decreases in body weight gain were observed during the first two weeks of the study for females from the 0.008% group and during the first week of the study for males from the 0.0033% and 0.008% groups. Other effects included increases in food consumption and decreases in efficiency of food utilization for females from the 0.008% group.

Clinical chemistry changes were mostly of border-line significance and not considered to be biologically significant. However, since glucose levels were increased in the high dose group in both studies as well as both sexes, this is considered an effect.

Statistically significant increases in the incidence of ovarian cysts were observed at the 0.004% and 0.008% treatment levels. Similarly, increases in bile duct proliferation were noted in the latter treatment levels.

The latency and prevalence of benign and malignant neoplasms were similar in control and monensin sodium-treated rats. There was no evident relationship between monensin sodium administration and cardiac and skeletal muscle lesions. Survival times were not affected.

In conclusion, the continued exposure of rats to diets containing up to 0.008% monensin sodium during in utero development and throughout

their lifetime did not produce a carcinogenic or oncogenic effect. However, based on variation in weight gain , ovarian cysts , increased glucose levels and bile duct proliferation, the no-observed- effect level is 33 ppm (1. 65 mg/kg/day).

3. Chronic Dog Study

   a. Title: "A One Year Chronic Toxicity Study of Mycelial Monensin Sodium Administered Orally to Beagle Dogs"

   b. Report Number: Study D- 3018

   c. Starting Date: January 18, 1978

   d. Ending Date : January 19, 1980

   e. Names and address of investigators who did the study:
   Dr. L. C. Howard and Dr. M. N. Novilla
   Lilly Research Laboratories
   Greenfield, Indiana 46140

   f. Name and address of laboratory where study was done:
   Toxicology Division
   Lilly Research Laboratories
   Division of Eli Lilly and Company
   Greenfield, Indiana 46140

   g. Study and Description and Conclusions:
   Groups of four male and four female beagle dogs were given daily oral doses of 0, 1.25, 2.5, 5 or 7.5 mg monensin sodium activity/kg (as mycelial monensin sodium) for one year. Dosing was accomplished by administering one-half of the dose in the morning and in the afternoon. All animals survived. Evidence of toxicity was observed at 5.0 and 7.5 mg/kg and included anorexia, hypoactivity and weakness, leg weakness, and weakness in neck musculature. These clinical signs occurred episodically with recovery occurring within several days after onset. Significant effects on body weight gain were observed at the three highest treatment levels. Growth was not retarded at the lowest level of 1.25 mg/kg/day.

   Prothrombin times in female dogs were significantly decreased at the 5.0 and 7.5 mg treatment levels at various times over the 52-week study. Other hematological parameters, such as the hematocrit, reticulocyte count, white blood cell and differential count, red blood cell count, MCH concentration and whole blood clotting time, were significantly altered at various times throughout the study. Although the effects appeared to be random in nature, they seemed to occur mainly in the two highest treatment groups.

   Alterations in clinical chemistry parameters directly related to monensin sodium administration were observed for dogs given 5.0 or 7.5 mg/kg and included elevations of CPK and ALT (SGPT). These elevations were transient in nature and returned to normal values with continued administration of monensin sodium. Monensin-related effects on urinalysis, organ weights, electrocardiograms and pathologic evaluation were not

observed. The effects noted in this study (clinical signs of toxicity and elevations in serum enzymes) were indicative of hepatic and/or muscle effects.

Based on body weight, clinical chemistries and clinical observations, this study supports a no-observed-effect level of 1.25 mg/kg/day .

4. Rat Reproduction/Teratology Study

   a. Title: "A Multi-Generation Reproduction Study with Monensin Sodium in the Wistar Rat" (with Teratology Component)

   b. Report Number: Studies R-78, R-958 and R- 29

   c. Starting Dates:
   R-78- January 31, 1978
   R-958 – August 30, 1978
   R-29 - January 9, 1979

   d. Termination Dates:
   R- 78 - September 15, 1978
   R-958 - January 24, 1979
   R- 29 - June 24, 1979

   e. Names and address of investigators who did the study:
   Dr. L. C. Howard, Dr. *N.* V. Owen and Dr. M. N. Novilla
   Lilly Research Laboratories
   Greenfield, Indiana 46140

   f. Name and address of laboratory where study was done:
   Toxicology Division
   Lilly Research Laboratories
   Division of Eli Lilly and Company
   Greenfield, Indiana 46140

   g. Study Description and Conclusions:
   Mycelial monensin sodium was administered continuously as a component of the diet to four successive generations of rats at level s of 0.0, 0.0033, 0.005 or 0.008% (monensin sodium activity). The reproductive performance of the adults and the health status and condition of delivered offspring of all generations and fetuses of F_2 generation parents were evaluated.

   Monensin did not have any effect on rat fertility, reproductive performance, gestation, sex ratio, or pup survival during lactation or survival after weaning. The only effect noted was a decreased weight gain of pups through lactation. This decreased weight gain continued through post weaning and mating. Monensin may have had an effect on lactation; however, since the animals continued to have a retarded weight gain after weaning, it was felt that it was a toxic effect due to monensin present in the milk and in the treated food consumed by the pups, especially since the decrease in weight gain was most evident after 14 days postpartum.

   A total of 247 pups that died and 1363 weanlings that survived,

encompassing all generations, were given a gross internal examination. Additionally, tissues of 42 controls and 134 treated weanlings (f_{3a}) were examined. There were no treatment- related conditions or lesions.

Based on this study, the reproductive no observed- effect level was 0.008% monensin activity or 4 mg/kg . However, based on the teratology study where the number of corpora lutea were significantly lower at the high dose level, a reproductive no- observed-effect level of 0.005% monensin activity or 2.5 mg/kg is supportable.

There were no treatment- related teratogenic effects observed in the teratology component of this study.

5. Rabbit Teratology Study

   a. Title: "A Teratology Study on Monensin Sodium in the Rabbit"

   b. Report Number: B- 7293

   c. Starting Date: October 7, 1973

   d. Termination Date: November 7, 1973

   e. Names and address of investigators who did the studies:
   F. 0. Gossett, J. K. Markham, E. R. Adams, N. V. Owen, S. S. Young and G. F. Kiplinger
   Lilly Research Laboratories
   Greenfield, Indiana 46140

   f. Name and address of laboratory where study was done:
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   g. Study Description and Conclusions:
   Groups of 15 pregnant Dutch Belted rabbits were given daily oral doses of 0.076, 0.38 or 0.76 mg/kg of monensin sodium on gestation days 6 through 18. On gestation day 28 the females were killed and evaluated for reproductive performance, and the fetuses were examined for abnormalities.

   Mean daily food consumption was reduced in all groups after dosing was initiated; however, the reduction at the high treatment dose was more marked. There was no other indication of treatment-related maternal toxicity. Deaths or abortions of 6 control and 4 monensin sodium-treated females occurred independently of treatment. The group values of the reproductive parameters and indices were normal, as were the values of fetal viability, sex distribution and weight. Developmental deviations were observed in a relatively small number of progeny with no evidence of treatment relationship.

   Monensin sodium administered to pregnant rabbits in oral doses as great as 0.76 mg/kg on gestation days 6 through 18, affected neither the

reproductive performance of the doe nor the development of the fetus. There was no evidence of a teratologic effect related to this treatment.

B. Safe Concentration of Residues:
A tissue residue study is included in PMF 5055, 51 FR 45555, December 19, 1986.

C. Metabolism and Total Residue Depletion Studies:
A tissue residue depletion study in goats is included in PMF 5055, 51 FR 45555, December 19, 1986.

VII. Agency Conclusions:

The data submitted in support of this supplemental NADA satisfy the requirements of Section 512 of the Act and demonstrate that RUMENSIN (monensin sodium) Premix (Type A medicated article) is safe and effective, when used in accordance with labeling directions, for the prevention of coccidiosis caused by *Eimeria crandallis*, *E. christenseni*, and *E. ninakohlyakimovae* in goats maintained in confinement.

The agency concludes that appropriate directions for use have been written for the proposed over-the-counter use of this premix in goats. The currently approved monensin premixes are codified in section 21 CFR 558.355 for use in chicken, turkey, and cattle.

According to the Center's supplemental approval policy (42 FR 64367, December 23, 1977), this is a Category II change. The agency further concludes from the information contained in the PMF 5055 that the approval of this supplement neither poses an increased human risk from exposure to the drug nor alters the condition of the drug's safety to the target animal species (goats). Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.