Date of Approval: 12-16-98

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 095-735

RUMENSIN® 80 Type A Medicated Article
(monensin sodium)

Sponsored by

ELANCO ANIMAL HEALTH

I. GENERAL INFORMATION

NADA Number: 095-735

Sponsor: Elanco Animal Health
A Division of Eli Lilly & Company
2001 W. Main Street
Greenfield, IN 46140

Established Name: monensin sodium

Trade Name: RUMENSIN® 80 Type A medicated article

Marketing Status: over-the-counter (OTC)

Effect of Supplement: Previously approved indications are discussed in the FOI SUMMARY for NADA 095-735. Type B and Type C medicated feeds containing monensin at 10 to 30 g/ton are approved for the prevention and control of coccidiosis caused by *Eimeria bovis* and *E. zuernii* in confined cattle.

This supplement provides for: (A) a lower effective dose based on body weight (0.14 to 0.42 mg/lb body weight/day) for the prevention and control of coccidiosis in feedlot cattle, pasture cattle (slaughter, stocker, feeder, and dairy and beef replacement heifers), and mature reproducing beef cows, and (B) the use of monensin at 10 to 200 g/ton for the prevention and control of coccidiosis in calves (except for veal calves) at a dose based on body weight (0.14 to 1.0 mg/lb body weight/day) up to a maximum of 200 mg/hd/day.

II. INDICATIONS FOR USE

Cattle: For improved feed efficiency in cattle fed in confinement for slaughter and mature reproducing beef cattle receiving supplemental feed, for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder, and dairy and beef replacement heifers), and for the prevention and control of coccidiosis caused by *Eimeria bovis* and *E. zuernii* in cattle fed in confinement, pasture cattle (slaughter, stocker, feeder, and dairy and beef replacement heifers), mature reproducing beef cows (on pasture or in dry lot), and calves.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. Dosage Form: RUMENSIN® 80 is a Type A medicated article available in a 50-lb. bag containing 80 g monensin sodium/lb.

B. Route of Administration: Orally, in feed.

C. Recommended Dosage for the Prevention and Control of Coccidiosis:

Feedlot Cattle: Feed continuously at the rate of 0.14 to 0.42 mg/lb body weight (bw)/day, depending on severity of challenge, up to a maximum of 360 mg/hd/day.

Pasture Cattle (slaughter, stocker, feeder, and dairy and beef replacement heifers): Feed at a rate to provide 0.14 to 0.42 mg/lb bw/day depending upon severity of challenge up to a maximum of 200 mg/hd/day. During the first 5 days, cattle should receive no more than 100 mg/day contained in not less than 1 lb feed.

Mature Reproducing Beef Cows: Feed at a rate to provide 0.14 to 0.42 mg/lb bw/day depending upon severity of challenge up to a maximum of 200 mg/hd/day. During the first 5 days, pastured cattle should receive no more than 100 mg/day contained in not less than 1 lb feed.

Calves (except for veal calves): Feed at a rate of 0.14 to 1.0 mg/lb bw/day, depending upon severity of challenge, up to a maximum of 200 mg/hd/day.

IV. EFFECTIVENESS

Effectiveness data collected in feedlot cattle for the approved indication for prevention and control of coccidiosis was determined to provide adequate evidence of the effectiveness of monensin for this same indication in mature reproducing beef cows and pasture cattle. Data supporting the effectiveness of previously approved indications are summarized in the FOI SUMMARY for NADA 095-735. Additional data was provided to satisfy concerns for an effective dose range in young animals.

A. Type of Study: an effective dose range confirmation study was conducted for the prevention and control of coccidiosis in calves by the following individual:

Kelly F. Lechtenberg, D.V.M, Ph.D.
Midwest Veterinary Services, Inc.
Oakland, NE 68045

B. General Design

1. Purpose: To determine the effective dose range of monensin for the prevention and control of coccidiosis in calves.

2. Animals and Housing: Ninety-six male Holstein calves (24/treatment group) were randomly assigned to building, location (blocks) within building, and treatment group; five died prior to treatment initiation. The 91 calves remaining were started on treatment at approximately 9.5 weeks of age.

3. Infections: One week following initiation of monensin feeding, calves were orally challenged with a total of approximately 300,000 oocysts/calf (approximately 231,000 *E. bovis* oocysts, 54,000 *E. zuernii* oocysts, and 15,000 miscellaneous *Eimeria* species). Infection was confirmed by fecal oocyst counts, fecal scores, and daily observations.

4. Dosage Form, Dose, and Route of Administration: Commercially available RUMENSIN® 80 Type A medicated article was incorporated into complete feeds at levels of 0, 10, 20, and 30 g/ton (90% dry matter basis) for oral administration. Feed was offered at levels corresponding to 0, 0.14, 0.28, and 0.42 mg/lb bw/day or 0, 25.1, 49.5, and 74.6 mg/hd/day. The duration of the trial was 35 days (7 days pre-challenge and 28 days post-challenge).

5. Parameters Measured: Primary efficacy variables were average daily body weight gain, fecal oocyst counts, and fecal scores. Secondary efficacy variables were gain efficiency and daily dry matter feed intake.

C. Results: Least squares means are summarized below in Table 4.1.

Table 4.1. Results expressed as least squares means.

	Monensin Level (mg/lb bw/day) [a]			
Variable	0	0.14	0.28	0.42
Average daily weight gain (lbs/day)	1.36	1.86	1.65	1.59
Total oocysts, $\log_{10}$ (oocyst/g feces/day)	1.47	0.42	0.31	0.22
E. bovis oocysts, $\log_{10}$ (oocyst/g feces/day)	1.40	0.39	0.29	0.19
E. zuernii oocysts, $\log_{10}$ (oocyst/g feces/day)	0.89	0.14	0.09	0.09
Fecal scores, square root (scale 0 to 4) [b]	0.22	0.13	0.16	0.12
Average daily intake (lbs dry matter/day)	4.45	4.63	4.56	4.63
Gain efficiency (lb gain/lb dry matter)	0.25	0.39	0.38	0.35
Mortality (number died/initial number) [c]	1/24	1/23	0/21	1/23

[a]Values for average daily gain, fecal scores, intake, and gain efficiency are treatment group least squares means averaging over weeks 1 through 4 post-challenge.

[b]0 = normal, 1 = slight diarrhea, 2 = diarrhea, 3 = diarrhea with blood, 4 = diarrhea with mucus and/or tissue

[c]Mortality data were not analyzed statistically.

Monensin prevented significant reduction in average daily gain at 0.14 mg/lb bw/day ($P = 0.004$). Oocyst counts in all treated groups were significantly reduced relative to controls ($P < 0.001$) with additional reduction in total oocyst counts and *E. bovis* counts at higher monensin doses. Although not statistically significant ($P > 0.05$), a numeric decrease in fecal scores occurred in all monensin treated groups relative to controls.

Among secondary efficacy variables, gain efficiency was significantly greater than controls at the 0.14 mg/lb bw/day dose level ($P = 0.009$) and was relatively constant at higher monensin levels. The efficacy demonstrated in both the primary and secondary variables occurred primarily during the third and fourth weeks post challenge, which coincided with clinical signs of coccidiosis.

D. Adverse Reactions: There were no adverse reactions to treatment.

E. Conclusions: The data support an effective dose range of 0.14 to 0.42 mg/lb bw/day of RUMENSIN® 80 for the prevention and control of infections of *Eimeria bovis* and *E. zuernii*.

V. ANIMAL SAFETY

Data supporting the target animal safety of previously approved indications for RUMENSIN® 80 Type A medicated article and this supplement are summarized in the FOI SUMMARY for NADA 095-735.

VI. HUMAN SAFETY

Data supporting the human food safety of RUMENSIN® 80 Type A medicated article are summarized in the FOI SUMMARY for NADA 095-735.

As part of the approval of this supplement, the Agency has taken the opportunity to update the human food safety information on this product and to codify an Acceptable Daily Intake (ADI) of 12.5 ug/kg bw/day.

VII. 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 demonstrate that RUMENSIN® 80 Type A medicated article is safe and effective for the indications stated on the product labeling.

An accurate diagnosis can be made with a reasonable degree of certainty by the layman and the directions and conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall retain over-the-counter marketing status.

In accordance with 21 CFR 514.106(b)(2)(iii), this is a Category II change that did not require a reevaluation of the safety or effectiveness data in the parent application. A tolerance of 0.05 ppm for negligible residues of monensin in the edible tissues of cattle and goats is codified at 21 CFR 556.420. The previously established ADI of 12.5 ug/kg bw/day is now codified. A withdrawal time before slaughter is not required.

In accordance with 21 CFR 25.33(a)(1) & (7), this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this supplemental 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 application and conducted or sponsored by the applicant. The THREE years of marketing exclusivity applies only to the new indication for a weight-based dose range for which the supplemental application was approved in calves.

RUMENSIN® 80 Type A medicated article is held by Elanco Animal Health under the following U.S. patent numbers:

Number	Expiration Date	Number	Expiration Date
4218438	02/14/99	4405609	01/22/01
4333919	09/12/99	4468380	08/28/01
4366168	09/21/01	4764534	08/16/05

VIII. APPROVED LABELING (attached)

Draft labeling is attached to this document.

A. Facsimile labeling for Type A medicated article:

- RUMENSIN® 80 Type A Medicated Article (monensin premix, USP)

B. Specimen labeling (Blue Bird label) for Type B medicated feeds:

- BLUEBIRD COCCI PELLET Type B Medicated Feed (300 to 2000 g/ton)
- BLUEBIRD MEDICATED CATTLE SUPPLEMENT Type B Medicated Feed (250 to 2000 g/ton)
- RUMENSIN® 80 Type B Medicated Feed for cattle maintained in confinement (100 to 1200 g/ton)
- RUMENSIN® 80 Type B Medicated Feed for pasture cattle (slaughter, stocker, feeder, and dairy and beef replacement heifers) (500 to 1200 g/ton)
- RUMENSIN® 80 Type B Medicated Feed for mature reproducing beef cows (on pasture or in dry lot) (500 to 1200 g/ton)

C. Specimen labeling (Blue Bird label) for Type C medicated feeds:

- RUMENSIN® 80 Type C Medicated Feed for cattle maintained in confinement (10 to 200 g/ton)
- RUMENSIN® 80 Type C Medicated Feed for pasture cattle (slaughter, stocker, feeder, and dairy and beef replacement heifers) (25 to 400 g/ton)
- RUMENSIN® 80 Type C Medicated Feed for mature reproducing beef cows (on pasture or in dry lot) (25 to 400 g/ton)
- RUMENSIN® 80 Type C Medicated Calf Feed (10 to 200 g/ton)