Date of Approval: September 5, 2013

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 095-735

RUMENSIN 90

Monensin

Type A medicated article to be used in the manufacture of Type B and C medicated feeds

Growing cattle on pasture or in dry lot (stocker and feeder cattle and dairy and beef replacement heifers)

This supplement provides for the reduction in the minimum concentration of monensin in Type C medicated feeds for growing cattle on pasture or in dry lot (stocker and feeder cattle and dairy and beef replacement heifers) from 25 to 15 grams per ton.

Sponsored by:

Elanco Animal Health

A Division of Eli Lilly & Co.

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I. GENERAL INFORMATION

A. File Number

NADA 095-735

B. Sponsor

Elanco Animal Health, A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

Drug Labeler Code: 000986

C. Proprietary Name

RUMENSIN 90

D. Established Name

Monensin

E. Pharmacological Category

Ionophore

F. Dosage Form:

Type A medicated article to be used in the manufacture of Type B and C medicated feeds

G. Amount of Active Ingredient

90.7 g/lb (200 g/kg)

H. How Supplied

25 kg bag; 600 kg tote

I. Dispensing Status

OTC

J. Dosage Regimen

For increased rate of weight gain: Feed at the rate of not less than 50 nor more than 200 mg per head per day in not less than one pound of Type C Medicated Feed; or after the 5th day, feed at the rate of 400 mg per head per day every other day in not less than 2 pounds of Type C Medicated Feed. The monensin concentration in the Type C Medicated Feed must be between 15 and 400 grams per ton. During the first 5 days, cattle should receive no more than 100 mg per day contained in not less than 1 pound of feed. Do not self feed.

Prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*: Feed at a rate to provide 0.14 to 0.42 mg per pound body weight per day,

depending upon severity of challenge, up to a maximum of 200 mg per head per day. The monensin concentration in Type C Medicated Feed must be between 15 and 400 g/ton. During the first 5 days, cattle should receive no more than 100 mg per day contained in not less than 1 pound of feed.

K. Route of Administration

Oral in feed

L. Species/Class

Growing cattle on pasture or in dry lot (stocker and feeder cattle and dairy and beef replacement heifers)

M. Indications

For increased rate of weight gain; for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing cattle on pasture or in dry lot (stocker and feeder cattle and dairy and beef replacement heifers).

N. Effect of Supplement

This supplement provides for the reduction in the minimum concentration of monensin in Type C medicated feeds for growing cattle on pasture or in dry lot (stocker and feeder cattle and dairy and beef replacement heifers) from 25 to 15 grams per ton.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage range. The Freedom of Information (FOI) Summary for the supplemental approval of NADA 095-735 dated November 18, 2005, contains dosage characterization information for replacement dairy heifers.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 095-735 dated November 18, 2005, contains a summary of studies that demonstrate effectiveness of the drug for replacement dairy heifers based on the similarities between animals and feeding regimes in those studies and today's growing replacement dairy heifers to allow the reduction in the minimum concentration of monensin in Type C medicated feeds for growing cattle on pasture or in dry lot (stocker and feeder cattle and dairy and beef replacement heifers) from 25 to 15 grams per ton. This change allows animals being fed a total mixed ration (TMR) consuming higher amounts of dry matter intake (DMI) to be in compliance with the RUMENSIN 90 approval for this class of cattle of providing 50 to 200 mg monensin per head per day.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 095-735 dated July 28, 1978

(FR 32749, Vol: 43, No. 146, July 28, 1978), and FOI Summary for the supplemental approval dated September 28, 1983 (FR 44204, Vol. 48, No. 189, September 28, 1983), contain summaries of target animal safety studies for pasture cattle (slaughter, stocker, and feeder cattle) and pasture cattle (dairy and beef replacement heifers), respectively.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

The Agency did not require additional information for microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summary for a supplemental approval dated December 1, 2006, contains a summary of all information used to assess microbial food safety (antimicrobial resistance) associated with the use of monensin in cattle. The Agency does not think that the nature of this supplement – reduction in the minimum concentration of monensin in Type C medicated feeds for growing cattle on pasture or in dry lot (stocker and feeder cattle, and dairy and beef replacement heifers) from 25 to 15 grams per ton – will impact antimicrobial resistance among bacteria of public health concern in or on treated cattle; therefore, additional evaluation of microbial food safety (antimicrobial resistance) is not warranted for this supplement.

B. Impact of Residues on Human Intestinal Flora:

Based on the firm's written assessment of the effects of monensin (RUMENSIN 90) residues present in the edible tissues of cattle treated with monensin at a maximum dose of 480 mg per head per day (40 grams per ton of monensin), the Agency concludes that the amount of monensin residues present in the human colon is too low to produce any adverse effects on human intestinal flora with respect to colonization barrier disruption or increases in populations of resistant bacteria. However, the step by step approach followed to determine the need to calculate a microbiological acceptable daily intake (mADI) for colonization barrier disruption in the human colon is described as follows:

1. Determination of the need for establishing a microbiological ADI

   a. Step 1: Are residues of the drug, and (or) its metabolites, microbiologically active against representatives of the human intestinal bacteria?

   Yes. Based on results from the firm's study AA9CUK0401 entitled "Activity of monensin against bacterial strains representing the normal human intestinal microbiota: determination of Minimum Inhibitory Concentration (MIC)," monensin has antimicrobial activity against representative human intestinal bacterial groups. A summary of study AA9CUK0401 is provided below.

   Title: "Activity of monensin against bacterial strains representing the normal human intestinal microbiota: determination of Minimum Inhibitory Concentration (MIC)"

   DWS Study No: 023/04
   DWS Protocol No: P1/023/04
   Report No: DWS/023/04
   Elanco Reference: AA9CUK0401

Study Director: Andrew Pridmore, BSc, PhD
Study Initiation (protocol approval): May 18, 2004
Experimental work commenced: May 21, 2004
Study Completion: July 19, 2004
GLP compliance: Study authors attest the study was conducted in compliance with OECD GLPs. Our review found acceptable compliance with FDA GLPs (21 CFR Part 58).

A minimum inhibitory concentration (MIC) of monensin was determined against 10 bacterial groups representing human intestinal flora. Isolates were obtained from fecal samples of healthy human volunteers that had not received antibiotics for three months. MIC testing was performed using standardized agar dilution MIC methodology as described by the Clinical and Laboratory Standards Institute (CLSI) and utilized quality control (QC) strains. An intra-study QC range was established to ensure reproducibility. The tests were done at two different inoculum levels: 109 and 105 CFU/mL. MIC_{50}, MIC_{90}, and geometric MICs were calculated for each bacterial group. With the exception of *Escherichia coli* and some isolates of *Lactobacillus*, most of the isolates were susceptible to monensin at the low inoculum concentration. At the high inoculum concentration, monensin did not show activity against *Bacteroides fragilis*, other *Bacteroides*, or *E. coli*; however, at low inoculum density, antibacterial activity was seen against the *Bacteroides* groups. Large inoculum effect, as evidenced by an increased MIC at higher inoculum level, was also seen in *Bifidobacterium*. A moderate inoculum effect was seen in *Fusobacterium*, *Clostridium*, *Eubacterium*, and *Lactobacillus* spp. In general, MIC testing showed that the growth of some human intestinal bacteria might be affected, which could potentially compromise the intestinal barrier if the drug concentration were to exceed a critical level. Therefore, the response to Step 1 in the guideline is YES, monensin does have microbiological activity against most representative human intestinal bacteria *in vitro*.

b. Step 2: Do residues enter the human colon?

Yes. Based on results from the studies presented by the firm, the amount of active monensin residues entering the human colon under the conditions of approval would be 12 µg. This value is determined considering the following information:

- Calculations were performed based on consumption of liver, which is the tissue with the highest concentration of monensin residues according to study T1F749401 (^{14}C-monensin study - described in the "Total Residue Study" section). The study shows a liver monensin concentration of 0.12 µg/g.
- Based on the consumption factor for liver of 100 grams/day, the amount of monensin residues entering the digestive tract would be 12 µg.

c. Step 3: Do the residues entering the human colon remain microbiologically active?

NO. The majority of monensin residues in the colon are bound to feces and are inactive. The concentration of free residues is too low to be effectively microbiologically active. The 12 µg of monensin entering the colon would

not remain microbiologically active because of dilution effects and fecal binding. Assuming a colonic mass of 220 grams, the final concentration of monensin residues in the colon would be 0.054 µg/mL. This concentration would not be microbiologically active because monensin would bind to fecal material. Based on results of the firm's study AA9CUK0402, the estimated binding of monensin could be 90%. Considering fecal binding of 90%, the free monensin that could interact with the intestinal flora would be 0.005 µg/mL (10% of 0.054 µg/mL). Therefore it is unlikely that the free monensin concentration in the human colon resulting from treatment at the proposed new dosage range in cattle is probably too low to produce any adverse effects on human intestinal flora.

A summary of study AA9CUK0402 is provided below:

Title: "Effect of faecal binding on antibacterial activity of monensin"

DWS Study No: 024/04
DWS Protocol No: P1/024/04
Report No: DWS/024/04
Study Director: Andrew Pridmore, BSc, PhD
Study Initiation (protocol issue): May 18, 2004
Experimental work commenced: June 23, 2004
Study Completion: July 3, 2004
GLP compliance: Study authors attest the study was conducted in compliance with OECD GLPs. Our review found acceptable compliance with FDA GLPs (21 CFR Part 58).

Monensin activity was determined using *Enterococcus faecalis* ATCC 29212 (DWC 9314) from the DWS culture collection (susceptible to monensin).

Monensin concentrations of 0, 1, 2, 5, 10, 20, 50, and 100 µg/mL were tested with 0, 10, 20, and 50% diluted feces from three separate donors. After monensin/fecal concentrations combinations were incubated for 0, 1, 2, and 6 hours, the supernatant was extracted after centrifugation, inoculated with the *E. faecalis* strain, and incubated for 48 hours. Antibacterial activity of each inoculated preparation was assessed by the presence or absence of bacterial growth. This provided an indication of the unbound monensin in each preparation. In the absence of feces, 10 µg/mL of monensin inhibited *E. faecalis* growth. With 10% fecal concentration, monensin activity was reduced at least by a factor of 10 (indicating 90% binding to feces).

The degree of binding increased when fecal concentration increased (for 2/3 fecal samples). All three fecal samples had maximal binding of monensin at 50% fecal concentration (>90% binding), and the binding occurred instantaneously while mixing the fecal dilutions with monensin. The 50% fecal concentration provided the closest representation of the *in vivo* situation. Therefore, it is concluded that the fecal binding of monensin residues to undiluted fecal material would likely exceed 90%.

The Agency concludes that the concentration of free monensin in the colon that could interact with intestinal bacteria is too low to produce any adverse effects on the human intestinal flora. Monensin residues are unlikely to disrupt the

colonization barrier of the human intestinal flora following consumption of edible products from cattle treated with up to 480 mg/head/day. Therefore, a mADI is not necessary for this product, under the conditions of use described above, at this time.

C. Toxicology:

CVM does not require any additional toxicology studies for this supplemental approval. The original approval of NADA 095-735 dated December 16, 1975 (40 FR 58289), supplemental approvals for NADA 095-735 (FOI summaries dated December 16, 1998, October 28, 2004, December 1, 2006, and November 18, 2011), and the original approval of NADA 038-878 dated May 20, 1975 (35 FR 7734) contain a summary of all toxicology studies and information for monensin.

D. Assignment of the Final ADI:

Data used to assess the impact of residues on human intestinal flora provided under the supplemental approval dated October 28, 2004, concluded that a mADI was not necessary. The final ADI is the toxicological ADI of 12.5 micrograms per kilogram of body weight per day. The codified ADI is listed under 21 CFR 556.420.

E. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable):

No reassessment of the safe concentrations for total monensin residues was needed for this supplemental approval. Safe concentrations for total monensin residues were established as part of the supplemental application for NADA 095-735 (FOI Summary dated October 28, 2004). The safe concentration of total monensin residues in each edible tissue of growing cattle is 1.5 ppm for muscle, 3.0 ppm for liver, 4.5 ppm for kidney, and 6.0 ppm for fat.

F. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 095-735 dated December 16, 1975 (40 FR 58289), and FOI Summary for the supplemental approval dated October 28, 2004, contain summaries of residue chemistry studies for cattle. Tolerances for residues of monensin in edible tissues of cattle are codified under 21 CFR 556.420: 0.10 ppm in liver; 0.05 ppm in muscle, kidney and fat; a tolerance is not required for milk.

G. Analytical Method for Residues:

The FOI Summaries for the original approval of NADA 095-735 dated December 16, 1975 (40 FR 58289), and for the supplemental approval dated October 28, 2004, contain the analytical method summaries for monensin in cattle.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to RUMENSIN 90:

NOT FOR HUMAN USE

Warning: When mixing and handling Rumensin 90, use protective clothing, impervious gloves and a dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse with water.

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 and 21 CFR part 514. The data demonstrate that RUMENSIN 90, when used according to the label, is safe and effective for increased rate of weight gain; for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in growing cattle on pasture or in dry lot (stocker and feeder cattle and dairy and beef replacement heifers). Additionally, data demonstrate that residues in food products derived from species treated with RUMENSIN 90 will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic 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)(1) or (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.