Date of Approval: December 1, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 095-735

RUMENSIN 80

Monensin
Type A Medicated Article
For Cattle Fed in Confinement for Slaughter

This supplement provides for an increase in the upper dose limit of monensin to 40 g/ton (480 mg/hd/day) in cattle being fed in confinement for slaughter for (1) improved feed efficiency and (2) prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*.

Sponsored by:

Elanco Animal Health

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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 80

D. Established Name: Monensin

E. Pharmacological Category: Ionophore/anticoccidial

F. Dosage Form: Type A Medicated Article

G. Amount of Active Ingredient: Monensin - 80 g per lb (176 g/kg)

H. How Supplied: 50 lb bag

I. How Dispensed: OTC

J. Dosage(s): Improved Feed Efficiency:

Feed monensin (RUMENSIN 80) at a dietary concentration of 5 to 40 g/ton* of feed (90% dry matter basis). Feed continuously in complete feed at a rate of 50 to 480 mg of monensin per head per day. *No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 g/ton (360 mg monensin per head per day).

Prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*:

Feed monensin (RUMENSIN 80) at a dietary concentration of 10 to 40 g/ton of feed (90% dry matter basis). Feed at a rate of 0.14 to 0.42 mg per lb of body weight per day, depending upon the severity of challenge, up to a maximum of 480 mg of monensin per head per day.

K. Route(s) of Administration: Oral in feed

L. Species/Class(es): Cattle fed in confinement for slaughter

M. Indication(s): 1) (5 to 40 g/ton*) - For improved feed efficiency.

*No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 g/ton (360 mg monensin per head per day).

2) (10 to 40 g/ton) - For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

N. Effect(s) of Supplement: This supplement provides for an increase in the upper dose limit of monensin to 40 g/ton (480 mg/hd/day) in cattle being fed in confinement for slaughter for (1) improved feed efficiency and (2) prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*.

II. EFFECTIVENESS:

A. Dosage Characterization:

Monensin was approved as a Type A Medicated Article for feedlot cattle at 5 to 30 g/ton for improved feed efficiency on December 16, 1975, and at 10 to 30 g/ton for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* on October 22, 1990. The maximum dose per animal for these indications was 360 mg monensin per head per day. (See Freedom of Information [FOI] Summaries for NADA 095-735 dated December 16, 1975, and October 22, 1990, respectively.)

The Animal Drug Availability Act of 1996 (ADAA) eliminated the requirement for dose optimization of a new animal drug. A dose or dose range is approvable up to a maximal dose that has been shown not to cause human or target animal safety concerns and does not depress animal response to the drug below that of the most efficacious dose [*Federal Register* 62(214):59832]. As a result of this provision, the studies supporting effectiveness of monensin for improved feed efficiency in the original approval were re-evaluated to increase the upper dose limit of monensin to 40 g/ton (480 mg per head per day).

Substantial evidence as codified in 21 CFR 514.4 (b)(2)(i) provides for the increase in the upper dose limit for a new animal drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. As a result of this provision, an increase in the upper

dose limit of monensin to 40 g/ton (480 mg per head per day) was evaluated for prevention and control of coccidiosis.

The term "cattle being fed in confinement for slaughter" is now used as the name of the class of cattle previously identified as "feedlot cattle."

B. Substantial Evidence:

1) Improved Feed Efficiency

The FOI Summary for the original approval of monensin for improved feed efficiency in cattle being fed in confinement for slaughter reported that the approved dosage range was 5 to 30 g/ton (see FOI Summary for NADA 095-735 dated December 16, 1975). The approval was based on results of 9 feeding trials conducted in 6 states (Arizona, Illinois, Indiana, Montana, Nebraska, and Texas) using 1582 cattle being fed in confinement for slaughter. Doses of monensin tested across all trials were: 0, 2.5, 5, 10, 20, 30, 40, and 80 g/ton. The trials used different types of cattle (sex, breed, and weight) fed different high concentrate rations (i.e., containing 50% or more grain). The monensin-fortified rations were introduced to the cattle at the assigned treatment level, i.e., cattle were not gradually stepped up to their assigned treatment level. The conditions under which these trials were conducted were considered typical of feedlots at that time and similar to those of current feedlots.

As a result of ADAA, results of the feeding trials were re-examined. There was no difference in feed efficiency of cattle fed 30 g/ton monensin compared to those fed 40 g/ton. However, feeding 40 g/ton monensin did improve feed efficiency when compared to controls. These results demonstrated that 40 g/ton monensin did not depress animal response below that of the previously determined most effective dose.

In conclusion, monensin fed at 40 g/ton of feed (90% dry matter) is effective at increasing feed efficiency in cattle being fed in confinement for slaughter. Product labeling indicates that no additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 g/ton (360 mg monensin per head per day).

2) Prevention and Control of Coccidiosis Due to *Eimeria bovis* and *Eimeria zuernii*

Substantial evidence as codified in 21 CFR 514.4 (b)(2)(i) provides for the increase in the upper dose limit for a new animal drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Substantial evidence must consist of at least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude that the new animal drug will be effective for the intended use at the lowest dose of the dose range suggested in the proposed labeling for that intended use. The FOI Summary for NADA 095-735 dated October 22, 1990, supports the effectiveness of monensin for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* at levels in the diet up to 40

g/ton of feed (90% dry matter) or up to 480 mg monensin per head per day in cattle being fed in confinement for slaughter.

III. TARGET ANIMAL SAFETY:

Target animal safety was established in the parent new animal drug application for monensin in cattle fed in confinement for slaughter (see FOI Summary for NADA 095-735 dated December 16, 1975). The maximum dose for the current approval (40 g/ton to deliver up to 480 mg/head/day) is below the maximum dose considered to be safe to target animals, based on conclusions from the safety data used to support the approval of December 16, 1975.

IV. HUMAN FOOD SAFETY:

This supplemental application is for the increased dose of monensin in cattle being fed in confinement for slaughter. FDA determined that the supplemental application needed only to address microbial food safety and microbial safety of monensin to human intestinal flora. All other human food safety information was derived from the original application (NADA 095-735, FR 58289-58290, Vol:40, No. 242, December 16, 1975) and subsequent applications (NADA 095-735, approved on October 28, 2004, NADA 38-878, 35FR 7734; May 20, 1970).

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for RUMENSIN 80 Type A medicated article for cattle fed in confinement for slaughter (NADA 095-735, FR 58289-58290, Vol:40, No. 242, December 16, 1975) and for COBAN (monensin) for poultry (NADA 38-878, 35 FR 7734; May 20, 1970) contains a summary of all toxicology studies. An ADI for monensin of 12.5 micrograms per kilogram of body weight was previously codified for monensin (21 CFR 556.420).

An assessment was presented on the effects of monensin residues present in edible tissues of cattle fed at the proposed upper level dose, on human intestinal flora. It was concluded that the amount of active monensin residues present in the human colon is probably too low to produce any adverse effect on the human intestinal flora.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

CVM did not require residue chemistry studies for this supplemental approval. The FOI summary for the supplemental approval of NADA 095-735 (approval date October 28, 2004) contains a summary of the residue chemistry studies.

2. Target Tissue and Marker Residue Assignment

The marker residue for monensin is parent monensin. A specific target tissue is not identified.

3. Tolerance Assignments

The codified tolerance for monensin in the edible tissues of cattle is 0.05 ppm (21 CFR 556.420).

4. Withdrawal Time(s)

Monensin is already approved for use in various classes of cattle fed up to 30 g monensin/ton with a zero withdrawal period. The data in Table 38 of the FOI Summary dated October 28, 2004, confirm the applicability of the zero withdrawal period for cattle fed up to 40 g monensin/ton. The total residues in the edible tissues are well below the safe concentrations.

C. Microbial Food Safety:

The sponsor submitted a written hazard characterization that followed the Agency's Guidance for Industry # 152 *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*. The Agency has determined that the hazard as characterized – zoonotic**,** pathogenic bacteria of public health concern from cattle treated with monensin, and resistant to monensin or other human use antimicrobials as a result of exposure to monensin – is not of a magnitude that warrants further microbial food safety assessment at this time.

D. Analytical Method for Residues:

The determinative HPLC method for detection of residues of monensin is available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The Material Safety Data Sheets (MSDS) for RUMENSIN Premix (including RUMENSIN 80) identify the potential for irritation of the skin, eyes, and respiratory tract through direct exposure and the potential for ingestion toxicity if consumed by humans. The labeling for RUMENSIN 80 Type A Medicated Article addresses these user safety concerns by indicating that the product is for animal feed only and by including the following Warning: "When mixing and handling Rumensin 80, 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 80, when used according to the label, is safe and effective for

Cattle Fed in Confinement for Slaughter:

1) (5 to 40 g/ton*) - For improved feed efficiency.

*No additional improvement in feed efficiency has been shown from feeding monensin at levels greater than 30 g/ton (360 mg monensin per head per day).

2) (10 to 40 g/ton) - For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.*

Additionally, data demonstrate that residues in food products derived from cattle fed in confinement for slaughter treated with RUMENSIN 80 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 required a reevaluation of the effectiveness and safety data in the original NADA (21 CFR §514.106(b)(2).

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:

RUMENSIN 80 Type A Medicated Article
Monensin Medicated Feedlot Cattle Feed Type B Medicated Feed
Monensin Medicated Feedlot Cattle Feed Liquid Type B Medicated Feed
Monensin Medicated Feedlot Cattle Feed Type C Medicated Feed (coccidiosis)
Monensin Medicated Feedlot Cattle Feed Type C Medicated Feed (feed efficiency)