Approval Date: December 15, 2005

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 095-735

Monensin Sodium (RUMENSIN 80)

Type A Medicated Article for Dairy Cattle

For increased milk production efficiency (production of marketable solids-corrected milk per unit of feed intake) in dairy cows.

This supplement to the NADA provides for use of RUMENSIN 80 in dairy cows in component feeding systems (including top dress).

Sponsored By:

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

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FREEDOM OF INFORMATION SUMMARY

RUMENSIN 80
Type A Medicated Article for Dairy Cattle

1. 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. Established Name:	Monensin sodium
d. Proprietary Name:	RUMENSIN 80
e. Dosage Form:	Type A medicated article
f. How Supplied:	50 lb bag
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Monensin sodium – 80 grams per pound (176 g/kg)
i. Route of Administration:	Oral in feed
j. Species/Class:	Dairy Cows
k. Recommended Dosage:	Component Feeding Systems (including top dress): Feed continuously to dry and lactating dairy cows a Type C medicated feed containing 11 to 400 g/ton monensin. The Type C medicated feed must be fed in a minimum of 1 lb of feed to provide 185 to 660 mg/head/day monensin to lactating cows or 115 to 410 mg/head/day monensin to dry cows. This provides cows with similar amounts of monensin they would receive by consuming total mixed rations containing 11 to 22 g/ton monensin on a 100% dry matter basis.
l. Pharmacological Category:	Ionophore
m. Indications:	For increased milk production efficiency

	(production of marketable solids-corrected milk per unit of feed intake).
n. Effect of Supplement:	This supplement to the NADA provides for use of RUMENSIN 80 in dairy cows in component feeding systems (including top dress).

2. EFFECTIVENESS:

a. Dosage Characterization

Dose characterization was performed as part of substantial evidence (see item 2.b below).

b. Substantial Evidence

Data described in the Freedom of Information (FOI) Summary for the parent new animal drug application for monensin in dairy cows approved October 28, 2004 (NADA 095-735), were used to establish effectiveness of monensin when used in component feeding systems (including top dress) for dairy cows. Data from this study, conducted with dairy cows fed monensin in total mixed rations (TMR), utilized daily dry matter intake (DMI) of individual cows (summarized on a weekly basis in lactation and dry periods), to determine daily monensin intake (mg/head/day). Cows were fed TMR containing 0, 8, 16, and 24 ppm monensin (100% dry matter basis). The approved range of monensin concentrations in TMR from the approval of October 28, 2004, was 12 to 24 ppm. Twelve (12) ppm was established as the low end of the approved range by use of non-overlapping confidence interval methods, see FOI Summary of October 28, 2004, approval. When monensin was expressed on a g/ton basis (100% dry matter basis), the tested doses were 0, 7, 15, and 22 g/ton, and the approved range was 11 to 22 g/ton. For purposes of data presentation in the current FOI Summary, monensin concentrations are expressed in ppm.

Monensin intakes were calculated by multiplying the mean daily DMI for each animal for each week of the study by the monensin dose. Data from the 16 and 24 ppm treatment groups were used to establish ranges in mg/head/day monensin intake. These two monensin concentrations were within the approved range of monensin concentrations, and DMI were not available at 12 ppm.

The measure of variability of monensin intakes employed was ± 2 standard deviations from the mean for the 16 and 24 ppm doses, and the ranges were calculated as follows:

1. Calculate the arithmetic mean (M) and standard deviation (STD) for each treatment group (16 and 24 ppm) from the average daily DMI during each week of the period for each animal.
2. Compute “Confidence Limits” (the plus/minus 2-standard deviation limits) with unit kg/head/day of DMI.
   $M_n \pm 2*STD_n$ for dose “n” ppm.
3. Compute “Confidence Limits” with unit mg/head/day of monensin.

$n*M_n \pm n*2*STD_n$ for dose n ppm.

4. The range of the monensin intake is from $(16*M_{16} - 16*2*STD_{16})$ to $(24*M_{24} + 24*2*STD_{24})$.

For calculating the ranges during lactation, DMI data were used for the standardized lactation period of the first on-study lactation (1 to 308 days in milk (DIM); see FOI Summary of October 28, 2004). For calculating ranges during the dry period, data were used from the first eight weeks following the first on-study lactation.

Results for the lactating cows are summarized in Table 2.1.

Table 2.1 Average Daily Dry Matter and Monensin Intake For the Standardized Lactation Period – Combined Parities

Variable	Monensin (ppm)	Average	STD	-2STD	+2STD
DMI (kg/head/day)	16	19.7	4.1	11.6	27.9
	24	19.5	4.0	11.6	27.4
Monensin Intake (mg/head/day)	16	315.6	65.3	185.0	446.3
	24	468.9	94.9	279.1	658.7

STD – Standard Deviation

During lactation, the range of monensin intakes from –2 STD for the 16 ppm dose to +2 STD for the 24 ppm dose was 185 to 659 mg/head/day.

Results for dry cows are summarized in Table 2.2.

Table 2.2 Average Daily Dry Matter and Monensin Intake During Weeks 1 to 8 of the Dry Period

Variable	Monensin (ppm)	Average	STD	-2STD	+2STD
DMI (kg/head/day)	16	12.6	2.7	7.2	17.9
	24	12.0	2.6	6.8	17.1
Monensin Intake (mg/head/day)	16	200.8	42.6	115.6	286.0
	24	286.8	61.6	163.6	410.0

STD – Standard Deviation

The range of monensin intakes from -2 STD for the 16ppm average to +2 STD for the 24ppm average was 116 to 410 mg/head/day.

The ranges in mg/head/day doses of monensin to dry and lactating cows necessitate a broad range of g/ton monensin concentrations in the Type C medicated feed for component feeding systems (including top dress). To this end, the sponsor proposed a range in monensin concentrations of 11 to 400 g/ton (as fed) in the Type C medicated feed for component feeding systems (including top dress). This proposal is supported by 1) U.S. approval for the use of Type C medicated feeds up to 400 g/ton for growing cattle (pasture and dry lot); and 2) ancillary studies supporting safe use in dairy cows with monensin concentrations in feed for component feeding and top dress of up to 450 ppm or approximately 400 g/ton (Van der Werf et al., 1998; Phipps et al., 2000). Therefore, the sponsor's proposal for the 11 to 400 g/ton monensin concentrations in the Type C medicated feed for component feeding systems (including top dress) is acceptable.

Given the above information, the approved label contains the following statement:

> *"Component Feeding Systems (including top dress): Feed continuously to dry and lactating dairy cows a Type C medicated feed containing 11 to 400 g/ton monensin. The Type C medicated feed must be fed in a minimum of 1 pound of feed per cow per day (Table 3) to provide 185 to 660 mg/head/day monensin to lactating cows or 115 to 410 mg/head/day monensin to dry cows. This provides cows with similar amounts of monensin they would receive by consuming total mixed rations containing 11 to 22 g/ton monensin on a 100% dry matter basis."*

References:

J.H.J. Van der Werf, L.J. Jonker and J.K. Oldenbroek. 1998. Effect of monensin on milk production by Holstein and Jersey cows. J. Dairy Sci. 81:427-433.

Phipps, R.H., J.I.D. Wilkinson, L.J. Jonker, M. Tarrant, A.K. Jones and A. Hodge. 2000. Effect of monensin on milk production of Holstein-Friesian dairy cows. J. Dairy Sci. 83:2789-2794.

3. TARGET ANIMAL SAFETY:

Target animal safety was established in the parent new animal drug application for monensin in dairy cows (See FOI Summary of the approval of October 28, 2004).

4. HUMAN SAFETY:

This supplemental application is for an alternative feeding method for the use of RUMENSIN 80 Type A Medicated Article (monensin sodium) in dairy cattle. No additional human food safety studies were required to support this supplemental approval because FDA determined that the human food safety information was available in the parent new animal drug application for monensin in dairy cows (See FOI Summary of the approval of October 28, 2004).

A. Toxicology:

An ADI for monensin of 12.5 micrograms per kilogram of body weight is codified for monensin (21 CFR 556.420).

Safe concentrations of 1.5, 3.0, 4.5, and 6.0 ppm were established for muscle, liver, kidney, and fat of cattle, respectively. The safe concentration of monensin in milk is 200 ppb.

B. Residue Chemistry

1. Residue Chemistry Studies

No additional residue chemistry studies were required for this supplemental approval. The residue study previously submitted to support the use of monensin in dairy cattle under NADA 095-735 reveals that the total residues in the edible tissues and milk at practical zero withdrawal were far below the safe concentrations when the cattle were dosed at 36g/ton. Therefore, FDA concluded that this alternative feeding method for the use of RUMENSIN 80 Type A Medicated Article (monensin sodium) in dairy cattle will not result in total residue concentrations in the tissues and milk of treated dairy cattle above the safe concentrations at the approved zero withdrawal.

2. Marker Residue and Target Tissue

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

3. Tolerance for the Marker Residue

The codified tolerance for monensin in the edible tissues of cattle is 0.05 ppm (21 CFR 556.420). Milk tolerance for monensin is not required.

4. Withdrawal Period

Neither a preslaughter withdrawal period nor a milk discard period is required for the use of monensin in dairy cows.

C. Microbial Food Safety

The Agency has considered the proposed supplement to allow top-dress or component feeding of monensin (RUMENSIN 80) to dairy cattle, and determined that a hazard (characterized as zoonotic, pathogenic bacteria of public health concern in or on dairy 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 requirement for a regulatory determinative method has been waived. However, the determinative HPLC method used to support the original monensin sodium applications is available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

E. User Safety Concerns:

User safety concerns associated with the effects of accidental inhalation or direct contact have been satisfactorily addressed by establishing label warnings. The bags of Type A medicated article, Type B medicated feed, and Type C medicated feed contain 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.

5. 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 of the implementing regulations. The data demonstrate that monensin sodium fed continuously as a component or top dress to dry and lactating dairy cows in a total diet containing 11 to 400 g/ton monensin, (185 to 660 mg/head/day to lactating or 115 to 410 mg/head/day to dry cows in a minimum of 1 lb of feed) is safe and effective for the claim indicated in section 1 of this FOI Summary. Component feeding (including top dress) in this manner provides cows with similar amounts of monensin they would receive by consuming total mixed rations containing 11 to 22 g/ton monensin (100% dry matter basis), the conditions provided for in the parent new animal drug approval for RUMENSIN 80 (NADA 095735) in dairy cows dated October 28, 2004.

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

Pursuant to 21 CFR 514.106 (b)(2)(i), this supplemental NADA approval is regarded as a Category II supplemental change which did require a reevaluation of safety and efficacy data in the parent NADA for dairy cattle.

The drug is to be fed in Type C medicated feeds in accordance with section 1 of the FOI Summary and the Blue Bird labeling that is attached to this document.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the drug product is assigned OTC status, and the labeling is adequate for the intended use.

No patent information was submitted by the sponsor with this application.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

RUMENSIN 80 Type A Medicated Article Label
Monensin Type B Dry Dairy Cattle Medicated Feed Label
Monensin Type B Liquid Dairy Cattle Medicated Feed Label
Monensin Type C Dairy Cattle Medicated Feed Label For Component Feeding System (Including Top Dress)
Monensin Type C Dairy Cattle Medicated Feed Label For Total Mixed Rations