Approval Date: March 6, 1976

Freedom of Information Summary
NADA 104-646

I. GENERAL INFORMATION:

NADA: 104-646
Sponsor: Elanco Products Company
A Division of Eli-Lilly & Company
P.O. Box 1750
Indianapolis, Indiana 46206

Generic Name: Monensin Sodium
Tylosin Phosphate
Trade Name: RUMENSIN ®
TYLAN ®

II. INDICATIONS FOR USE

For improved feed efficiency and for the reduction of incidence of liver abscesses in beef cattle caused by *Sphaerophorus necrophorus and Corynebacterium pyogenes.*

III. DOSAGE:

A. DOSAGE FORM	Feed
B. ROUTE OF ADMINISTRATION	Oral
C. RECOMMENDED DOSAGES:	
Monensin	10 through 30 g/ton
Tylosin	10 g/ton

IV. EFFECTIVENESS:

Compliance with Combination Policy

The sole claim for tylosin is for a reduction in the incidence of liver abscesses. A reduction in incidence occurred in each experiment The sole claim for monensin is for an improvement in feed efficiency. Such an improvement occurred in every experiment. Monensin did not interfere with the tylosin activity in regard to reduction of liver abscesses. Tylosin did not interfere with monensin activity in regard to improved feed efficiency. Thus, the use of the two drugs are in complete compliance with the combination drug policy.

All studies were well-controlled placebo versus treatment experiments. The design was

a 2 x 4 factorial study.

A. 306-739-4-16

Cooperators:

Lloyd Sherrod and Rick Kellison
Texas Tech University
Center at Amarillo
Pantex, Texas

Monitors:

N.G. Elliston and H. Brown
Lilly Research Laboratories
Greenfield, Indiana

SUMMARY:

Two hundred steers weighing approximately 625 lbs. were used in this 140-day experiment to study the effect of feeding monensin for improving feed efficiency and of feeding tylosin for the prevention of liver abscesses. The ration treatment programs were 0, 5, 20 and 30 g/ton monensin with and without 10 g/ton tylosin. The ration was a complete mixed meal ration containing approximately 80 percent steam-flaked milo, 10 percent cottonseed. hulls and 10 percent supplement.

Average daily gain and feed efficiency main effects for 0, 5, 20 and 30 g/ton monensin respectively were 3.46, 7.18, 3.63, 7.67, 3.56, 6.86, 3.51 and 6.47. Monensin was effective in improving feed conversion and feed conversion was not altered by tylosin treatment. There were no abscessed livers in any of. the tylosin treatments while-7% of the livers in the treatments not receiving tylosin were abscessed Liver abscess incidence was not affected by monensin treatment. There were no differences in carcass measurements. All steers were 6 to 9months of age.

(Eds. Note: The following table consists of 7 columns.)

SUMMARY OF THE MAIN EFFECTS

Tylosin (g/ton)		Monensin (g/ton.) 0	5	20	30	Av.
0	ADG, lbs.	3.53	3.57	3.62	3.45	3.54
	ADF, lbs.	25.85	27.75	24.87	21.90	25.09
	F/G, lbs.	7.31	7.77	6.88	6.35	7.08
	Abscessed livers/No. cattle	2/20	4/20-	1/30	0/30	7/100

10	ADG, lbs.	3.38	3.70	3.51.	3.57	3.54
	ADF, lbs.	23.80	27.95	23.97	23.53	24.81
	F/G, lbs.	7.05-	7.56	6.83	6.60	7.01
	Abscessed livers/No. cattle	0/20	0/20	0/30	0/30	0/100
Av.	ADG, lbs.	3.46	3.63	3.56	3.51	
	ADF, lbs.	24.82	27.85	24.42	22.72	
	F/G, lbs.	7.18	7.67	6.86	6.47	
	Abscessed livers/No cattle	2/40	4/40	1/60	0/60	

B. 306-739-4-20

Cooperator:

Stanley D. Farlin
University of Nebraska
Lincoln, Nebraska

Monitors:

H.P. Grueter and H. Brown
Lilly Research Laboratories
Greenfield, Indiana

SUMMARY:

A total of 383 finishing steers weighing approximately 660 lbs. each were fed a high moisture corn ration for 90 days to evaluate the effects of 0, 5, 20 and 30 g/ton monensin with and without 10 g/ton tylosin. The main effects of monensin for feed per pound of gain were 7.14, 6.94, 6.98 and 6.42 respectively for 0, 5, 20 and 30 g/ton. Tylosin reduced the incidence of abscessed livers from 59 of 190 for control to 36 of 187. Tylosin also improved feed efficiency from 7.04 for control to 6.71. Monensin had no effect on incidence of liver abscesses or average daily gain except 5 g/ton monensin increased average daily gain by 4%. All steers were 6 to 9 months old and typical animals for feedlot use. All steers were implanted with SYNOVEX-S on day 30 of the study.

(Eds. Note: The following table consists of 7 columns.)

SUMMARY OF THE MAIN EFFECTS

Tylosin (g/ton).		Monensin (g/ton) 0	5	20	30	Av.
0	ADG, lbs.	3.02	3.16	3.02	2.84	3.01
	ADF, lbs.	22.00	22.70	21.15	18.75	21.15

	F/G, lbs	7.30	7.18	7.06	6.60	7.04
	Abscessed livers/.No. Cattle	15/48	12/48	16/47	16/47	59/190
10	ADG, lbs.	3.09	3.21	2.99	3.05	3.08
	ADF, lbs.	21.60	21.50	20.55	19.00	20.66
	F/G, lbs.	6.99	6.71	6.90	6.24	6.71
	Abscessed livers/No. Cattle	10/46	12/47	5/48	9/46	36/187
	Av. ADG, lbs.	3.05	3.18	3.00	2.94	
	ADF, lbs.	21.80	20.07	20.94	18.87	
	F/G, lbs.	7.14	6.94	6.98	6.42	
	Abscessed livers/No. Cattle	25/94	24/95	21/95	25/93	

Rations (as fed basis) fed during study were as follows:

	Corn Silage	High-Moisture Corn	Supplement
1st 5 days	83.7%	13.9%	2.32%
5 to 10 days	68.5%	28.8%	2.67%
10 to 14 days	48.2%	48.6%	3.14%
Final Ration	10% alfalfa-brome hay	85%	5%

C. 306-739-4-21

Cooperator:

E.E. Hatfield
University of Illinois
Urbana, Illinois

Monitors:

R.D. Olson and H. Brown
Lilly Research Laboratories
Greenfield, Indiana

SUMMARY:

One hundred ninety-two Holstein steers weighing approximately 590 lbs. were used in this 223-day experiment to test the compatibility of feeding monensin for improving feed efficiency and feeding tylosin for the prevention of liver abscesses. In addition, two sources of protein, alfalfa haylage and soybean meal were evaluated. The ration treatment programs were 0, 5, 20 and 30 g/ton monensin with and without 10 g/ton

tylosin. The grain source was cracked corn and the final ration contained approximately 80% concentrate and 20% roughage. The alfalfa haylage and soybean meal protein supplements were formulated to contain the same level of fiber and to be isonitrogenous. Average daily gain and feed efficiency main effects for 0, 5, 20 and 30 g/ton monensin respectively were 2.65, 7.67, 2.77, 7.32, 2.83, 7.14, 2.90 and 6.88. Average daily gain and. feed efficiency main effects for 0 and 10 g/ton tylosin were 2.75, 7.34, 2.83 and 7.17 respectively. There were 8.33% of the livers condemned for abscesses in the treatments without tylosin and 6.25% of the livers condemned for abscesses in treatments with tylosin.

(Eds. Note: The following table consists of 7 columns.)

SUMMARY OF THE MAIN EFFECTS

Tylosin		----------Monensin (g/ton)----------				
(g/ton).		0	5	20	30	Av.
0	ADG, lbs.	2.59	2.75	2.83	2.82	2.75
	ADF, lbs.	20.30	20.25	20.13	19.83	20.13
	F/G, lbs.	7.85	7.38	7.11	7.03	7.34
	Abscessed livers/No ..					
	Cattle	0/24	1/24	2/24	5/24	8/96
10	ADG, lbs.	2.71	2.79	2.83	2.97	2.83
	ADF, lbs.	20.25	20.23	20.20	20.03	20.18
	F/G, lbs.	7.49	7.26	7.17	6.74	7.17
	Abscessed livers/No					
	Cattle	3/24	1/24	1/24	1/24	6/96
Av.	ADG, lbs.	2.65	2.77	2.83	2.90	
	ADF, lbs.	20.28	20.24	20.16	19.93	
	F/G, lbs.	7.68	7.32	7.14	6.88	
	Abscessed livers/No.					
	Cattle	3/48	2/48	3/48	6/48	

D. 306-739-4-25

Cooperator:

Dr. J.K. Matsushima
Colorado State University
Ft. Collins, Colorado

Monitors:

J.W. McAskill and H. Brown
Lilly Research Laboratories
Greenfield,Indiana

SUMMARY:

The effect of 0, 5, 20 and 30 g/ton monensin alone and in combination with 10 g/ton tylosin upon feedlot performance was studied during a 142-day finishing trial using 216 yearling cattle weighing approximately 600 lbs. each. Two pens of eighteen cattle each were used on the 0 and 30 g/ton levels while one pen of 18 cattle was used on the 5 and 20 g/ton levels, both alone and in combination with 10 g/ton tylosin. Feed efficiency was improved by the 30 g/ton monensin treatment with and without tylosin. The 20 g/ton monensin treatment also improved feed efficiency when fed in combination with tylosin. Gain was not affected by treatment. Tylosin had no apparent effect upon performance in this study, but was highly effective in controlling liver abscess. Incidence of abscessed livers was 61% vs. 4.9% for non-tylosin and tylosin cattle respectively, ($P < 0.001$). Carcass quality was not affected by treatment. There were 8.33% of the livers condemned for abscesses in the treatments without tylosin and 6.25% of the livers condemned for abscesses in treatments with tylosin. All cattle were implanted with SYNOVEX. Tylosin and monensin were both effective in improving feed efficiency, and the responses of the two appeared to be additive.

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E. T1F537615

Cooperators:

W.W. Heinemann and E.M. Hanks
Washington State University,
Irrigated Agriculture Research and Extension Center
Prosser, Washington 99350

Monitor:

Dr. D.C. Young.
Lilly Research Laboratories
Greenfield, Indiana 46140

SUMMARY:

One hundred seventy-six Hereford-Angus crossbred steers weighing approximately 780 pounds were used in this 127-day feeding study. The cattle were implanted with SYNOVEX and fed a 66-percent corn ration.

(Eds. Note: The following table consists of 7 columns.)

----Treatment-----						
Monensin	Tylosin	No.	Av. Daily Gain	Av. Daily DMI	DMI/	Liver Abscesses

		Pens	(Lbs.)	(Lbs.)	Gain	No./Cattle
0	0	2	3.13	22.41	7.18	3/20
0	10	2	3.17	22.29	7.04	3/22
5	0	2	3.28	22.01	6.72	6/21
5	10	2	3.23	21.82	6.76	2/22
10	0	2	3.28	22.07	6.74	9/22
10	10	2	3.14	21.08	6.73	2/22
30	0	2	2.89	19.85	6.86	11/22
30	10	2	3.11	20.61	6.63	2/22

Monensin decreased the dry matter (feed) required for gain in both the non-tylosin and tylosin-fed groups. Tylosin reduced the incidence of liver abscesses. Monensin increased liver abscesses when tylosin was not fed. All cattle were typical for starting feedlot animals and were approximately 9 to 12 months of age.

V. ANIMAL SAFETY:

VPR-289-766

A Monensin Tylosin combination Toxicity Study. in Cattle

Monitors:

R.L. VanDuyn, H.K. Cohen and R.P. Rathmacher
Lilly Research Laboratories
Greenfield, Indiana

SUMMARY:

Hereford cattle were fed the combination of monensin and tylosin at 30 and 10, 90 and 30, and 150 and 50.g/ton of complete feed, respectively, for approximately 160 days to determine the safety of the combination for cattle.

All cattle-but one, a control animal, survived the 160-day feeding period. No gross or microscopic treatment associated changes were observed in the cattle at necropsy. There were no changes in serum chemistry, hematology, and urinalysis values which were regarded as being indicative of toxicity. A dose associated decrease in performance occurred during the first 56 days of feeding, but the.cattle accommodated to the treatment and performance was as good as or better than controls for the remaining feeding time. It was concluded from this study, that the combination of monensin and tylosin could be fed at levels of 30 and 10 g/ton in complete feed with a 5X margin of safety.

MONENSIN TYLOSIN CATTLE SAFETY STUDY

VPR-289-766

Performance Data

Treatment (g/ton) Monensin	Tylosin	ADG 1/ (lbs.)	ADF 2/ (lbs.)	Feed/ Gain
		-------0-56 Day period--------		
0 0	1.89	24.9	13.60	
30	10	1.49	17.6	11.97
90	30	0.44	10.0	23.28
150	50	0.84	7.3	
		--------56-112 Day Period------		
0	0	2.50	25.3	10.20
30	10	2.52	21.2	8.42
90	30	2.62	16.8	6.52
150	50	2.57	13.3	5.24
		------112-159 Day Period------		
0	0	1.31	15.4	13.23
30	10	1.96	15.4	7.88
90	30	1.51	13.4	9.22
50	50	1.32	10.6	7.88
		-------0-159 Day Period-------		
0 0	1.93	22.2	11.63	
30	10	1.99	18.3	9.20
90	30	1.52	13.4	8.76
150	50	1.00	10.4	10.36

1/ Average daily gain
2/ Average daily feed

The proposed use of these two drugs is for the rations of feedlot beef cattle being fed in confinement for slaughter. There is no concern for effects on reproduction in this class of animal.

VI. HUMAN SAFETY:

T1F317609

Investigator

Dr. S. Farlin
University of Nebraska
Lincoln, Nebraska

Monitors:

Dr. C. Parrott and Dr.H. Grueter
Eli Lilly and Company
Omaha, Nebraska 28103

Assays:
Dr. Paul Handy
Eli Lilly Research Laboratories
Greenfield, Indiana

Tissue Residue Analysis Tylosin Plus Monensin in Feedlot Cattle

SUMMARY:

Feedlot cattle were fed rations containing tylosin (10 g/ton) and monensin (30 g/ton) for 141 days. Selected animals were fed an additional two days with medicated and/or non-medicated feed to provide 0, 24 and 48-hour withdrawal samples. No detectable residues of either tylosin or monensin were found in any of the tissues assayed. The assay sensitivities were <0.l ppm for tylosin and <0.04 ppm for monensin.

EXPERIMENTAL PROCEDURE:

Design:

One hundred ninety-two steers were randomly allotted to four treatments: 1) control, 2) 10 g/ton tylosin, 3) 30 g/ton monensin and 4) 10 g/ton tylosin plus 30 g/ton monensin. Each treatment consisted of two replications with 24 steers per replicate. The efficacy portion of this experiment continued for 141 days. Selected cattle were slaughtered two days after the conclusion of the efficacy study so that tissue samples for 24 and 48-hour withdrawal intervals were available for the safety study. Since there were no drug residues in any tissue at "0" day withdrawal, absolute human safety is assured.

The regulatory analytical methods for detection of residues of the drug are filed in the Food Additives Analytical Manual on display in the Public Records and Document Center, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20852.

VII. AGENCY CONCLUSIONS:

The Food and Drug Administration has concluded that when used as directed monensin and tylosin will be safe and effective for the claims in compliance with Section 512 of the ACT.

VIII. LABELING (Attached)

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

FOI Summary; NADA 106-646(original); RUMENSIN ®/TYLAN ® (Monensin Sodium/ Tylosin Phosphate); March 6, 1976
--Editor's abstract

1 General Information:

ORIGINAL APPLICATION
21 CFR PART 514

Identification:

NADA P
SUBPART.A, § 514.1
Date:

Name of Applicant:

Chemical Name: See § 138.2 of Title 21 CFR
Generic Name:

Proprietary:

Generic Name:

Proprietary:

2. Indications for use:

3 Dosage Form:

Route of Administration:

Recommended Dosage: