Date of Approval: August 1, 2012

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-343

PULMOTIL 90 and RUMENSIN 90

Tilmicosin Phosphate and Monensin
Type A Medicated Articles to be Used in the Manufacture of
Type B and C Medicated Feeds
Cattle Fed in Confinement for Slaughter

1) For prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* and control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of cattle fed in confinement for slaughter, where active BRD has been diagnosed in at least 10% of the animals in the group.

2) For improved feed efficiency and control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of cattle fed in confinement for slaughter, where active BRD has been diagnosed in at least 10% of the animals in the group.

Sponsored by:

Elanco Animal Health, A Division of Eli Lilly & Co.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-343
B. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
C. Proprietary Names:	PULMOTIL 90 and RUMENSIN 90
D. Established Names:	Tilmicosin phosphate and monensin
E. Pharmacological Categories:	Tilmicosin phosphate – antimicrobial Monensin – ionophone
F. Dosage Form:	Type A medicated articles to be used in the manufacture of Type B and C medicated feeds
G. Amount of Active Ingredients:	Tilmicosin phosphate – 90.7 g/lb Monensin – 90.7 g/lb
H. How Supplied:	PULMOTIL 90 – 22 lb (10 kg) bag RUMENSIN 90 – 50 lb (22.68 kg) bag
I. How Dispensed:	VFD
J. Dosage:	<u>Coccidiosis and BRD</u>: Tilmicosin phosphate - 568 to 757 g/ton* Monensin – 10 to 40 g/ton** <u>Feed efficiency and BRD</u>: Tilmicosin phosphate - 568 to 757 g/ton* Monensin – 5 to 40 g/ton** *100% dry matter basis **90% dry matter basis
K. Route of Administration:	Oral, in feed
L. Species/Classes:	Cattle fed in confinement for slaughter

M. Indications:

1) For prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* and control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of cattle fed in confinement for slaughter, where active BRD has been diagnosed in at least 10% of the animals in the group.

2) For improved feed efficiency and control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of cattle fed in confinement for slaughter, where active BRD has been diagnosed in at least 10% of the animals in the group.

II. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act (ADAA) of 1996, if the animal drugs or active ingredients intended for use in combination in an animal feed have already been separately approved for the particular uses and conditions for which they are intended for use in combination, the Center for Veterinary Medicine (CVM) will not refuse to approve an NADA for the combination on effectiveness grounds unless the FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness
- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Tilmicosin phosphate, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in feed for beef and non-lactating dairy cattle for control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group (21 CFR 558.618(e)(2)). Monensin, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately

approved for use in feed for cattle fed in confinement for slaughter at 10 to 40 g/ton for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* (21 CFR 558.355(e)(3)(vii)) and at 5 to 40 g/ton for improved feed efficiency (21 CFR 558.355(e)(3)(i)). Effectiveness of each drug, tilmicosin phosphate and monensin when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health, A Division of Eli Lilly & Co.'s approved NADAs 141-064 and 095-735 for tilmicosin phosphate and monensin, respectively.

Because tilmicosin phosphate and monensin each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that tilmicosin phosphate plus monensin provide appropriate concurrent use for the intended target population. The use of tilmicosin phosphate plus monensin provides appropriate concurrent use because these drugs are intended to treat different conditions (BRD, coccidiosis and feed efficiency) likely to occur simultaneously with sufficient frequency in cattle fed in confinement for slaughter. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed.

III. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on target animal safety grounds unless:

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and CVM finds that the application fails to show that the combination is safe, or
- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and CVM finds that the application fails to show that the combination is safe.

Tilmicosin phosphate, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in feed for beef and non-lactating dairy cattle for control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group (21 CFR 558.618(e)(2)). Monensin, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in feed for cattle fed in confinement for slaughter at 10 to 40 g/ton for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* (21 CFR 558.355(e)(3)(vii)) and at 5 to 40 g/ton for improved feed efficiency (21 CFR 558.355(e)(3)(i)).

Under the provisions of ADAA, this original approval allows for the combination of tilmicosin phosphate (as provided by Elanco Animal Health, A Division of Eli Lilly & Co.), and monensin (as provided by Elanco Animal Health, A Division of Eli Lilly & Co.). Target animal safety for each drug, tilmicosin phosphate and monensin when administered alone in accordance with its approved uses and conditions of use, is

demonstrated in Elanco Animal Health, A Division of Eli Lilly & Co.'s approved NADAs 141-064 and 095-735 for tilmicosin phosphate and monensin, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of tilmicosin phosphate and monensin when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Therefore, in accordance with the FFDCA, as amended by the ADAA of 1996, no specific target animal safety studies are required for approval of this application.

IV. HUMAN FOOD SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or
- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Toxicology:

Safety of the individual drugs in this combination product has been established by data in NADA 140-929 for tilmicosin (FOI Summary dated March 24, 1992), NADA 095-735 for monensin (FOI Summary dated December 16, 1975), and NADA 038-878 for monensin (FOI Summary dated May 20, 1970).

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Studies

CVM did not require total residue and metabolism studies for this approval. The FOI Summaries for the original approval of NADA 140-929 dated March 3, 1992, and the supplemental approval of NADA 141-064 dated April 19, 2011, contain summaries of total residue and metabolism studies for tilmicosin in cattle. Total residue and metabolism studies for monensin in cattle are contained in NADA 095-735 (40 FR 58289, December 16, 1975).

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval. The FOI Summary for the original approval of NADA 140-929 dated March 3, 1992, contains a summary of comparative metabolism studies

for tilmicosin in cattle. Comparative metabolism studies for monensin in cattle are contained in NADA 095-735 (40 FR 58289, December 16, 1975).

c. Tissue Residue Depletion Study

Study Title - ***"Non-Clinical Laboratory Study (GLP): Residue Depletion in Cattle Following Oral Administration of Tilmicosin and Monensin when Administered in the Feed to Cattle for 14 Days" -- Study No.: T5C310720***

Study Director: Teresa Schieber, D.V.M., Midwest Veterinary Services, Oakland, NE.

Study Location:
In-life Phase--Midwest Veterinary Services, Oakland, NE.
Analytical Phase—Covance Laboratories, Inc., Madison, WI.

Animals: Thirteen steers and thirteen heifers approximately 8-9 months of age weighing 228.5 kg to 277.5 kg on Study Day -1.

Test Substance:
PULMOTIL 90 Type A Medicated Article and RUMENSIN 90 Type A Medicated Article administered in a Type C medicated complete feed for 14 consecutive days. Treatment Groups and Study Design:

Animals were assigned to one of three treatment groups on Study Day -1 as shown in Table 1. Tilmicosin was administered at the target rate of 757 g/ton and monensin at the target rate of 40 g/ton.

Table 1. Treatment Design

Treatment Group	Total No. of Animals	Tilmicosin Target Dose (g/ton)	Monensin Target Dose (g/ton)	Administration Duration (days)	Slaughter and Liver Tissue Sample Collection Time
01	2 (1 steer and 1 heifer)	0	0	0	Study day -1
02	10 (5 steers and 5 heifers)	757	40	14	12 hrs post treatment
03	10 (5 steers and 5 heifers)	757	40	14	28 days post treatment

Tissue Residue Analysis: Parent tilmicosin concentrations in liver samples were determined by the official regulatory method. Monensin residue concentrations in liver were determined by the official regulatory method.

Results:

1. Monensin Residue Concentrations in Liver

Using the official regulatory method, only one animal (#40) had a residue concentration above 0.06 ppm, which was the upper limit of the method.

2. Parent Tilmicosin Residue Concentrations in Liver

Table 2. Tilmicosin Concentration in Liver

Animal Identification	Treatment Group	Tilmicosin (ppm)
04	T01	<0.0600
25	T01	<0.0600
05	T03	<0.0600
09	T03	0.0649
11	T03	0.106
15	T03	<0.0600
17	T03	0.0875
24	T03	<0.0600
34	T03	<0.0600
35	T03	<0.0600
42	T03	0.120
46	T03	0.201

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2. Target Tissue and Marker Residue Assignment

No reassessment of target tissue and marker residue was needed for this approval. The FOI Summaries for the original approval of NADA 140-929 and NADA 095-735 contain summaries of information used to determine the target tissue and marker residue.

3. Tolerance Assignments

The tolerance for parent tilmicosin in liver of cattle is 1.2 ppm (21 CFR 556.735).

The tolerance for monensin in liver of cattle is 0.1 ppm (21 CFR 556.420).

4. Withdrawal Time

A 28-day withdrawal is assigned for cattle treated with tilmicosin in combination with monensin.

C. Microbial Food Safety:

1. Antimicrobial Resistance

With respect to the human food safety evaluation for these types of combination new animal drug approvals, the agency is permitted only to evaluate whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs of the combination interferes with the methods of analysis of another active ingredient or drug in the combination (section 512(d)(4)(A) of the Federal Food, Drug, and Cosmetic Act). Therefore, we did not assess the impact of this combination of tilmicosin and monensin on antimicrobial resistance development among bacteria of public health concern in or on treated cattle fed in confinement for slaughter.

2. Impact of Residues on Human Intestinal Flora

With respect to the human food safety evaluation for these types of combination new animal drug approvals, the agency is permitted only to evaluate whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs of the combination interferes with the methods of analysis of another active ingredient or drug in the combination (section 512(d)(4)(A) of the Federal Food, Drug, and Cosmetic Act). Therefore, we did not assess the impact of this combination of tilmicosin and monensin on the residues of tilmicosin and monensin in edible food products from treated cattle fed in confinement for slaughter on human intestinal flora and the need to establish a microbiological acceptable daily intake.

D. Analytical Method for Residues:

1. Determinative Method

The FOI Summary for the original approval of NADA 140-929 dated March 3, 1992, contains the analytical method summaries for tilmicosin in cattle. NADA 095-735 (40 FR 58289, December 16, 1975) contains the analytical method summaries for monensin in cattle. Method non-interference for the analysis of monensin in the presence of tilmicosin and the analysis of tilmicosin in the presence of monensin has been established for the determination of the withdrawal period for the combination use of PULMOTIL 90 and RUMENSIN 90 in cattle.

2. Confirmatory Method

The FOI Summary for the original approval of NADA 140-929 dated March 3, 1992, contains the analytical method summaries for tilmicosin in cattle. NADA 095-735 (40 FR 58289, December 16, 1975) contains the analytical method summaries for monensin in cattle. Method non-interference for the analysis of monensin in the presence of tilmicosin and the analysis of tilmicosin in the presence of monensin has been established for the determination of the withdrawal period for the combination use of PULMOTIL 90 and RUMENSIN 90 in cattle.

3. Availability of Method

The methods are available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type B and C medicated feed:

User Safety Warnings: Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling PULMOTIL 90 and RUMENSIN 90 should use protective clothing, impervious gloves, goggles, and a NIOSH-approved dusk mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a Material Safety Data Sheet, call 1-800-428-4441.

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 contained in the previously approved NADAs for PULMOTIL 90 and RUMENSIN 90 demonstrate that, when they are used according to the label, they are safe and effective for

1) Prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* and control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of cattle fed in confinement for slaughter, where active BRD has been diagnosed in at least 10% of the animals in the group.

2) Improved feed efficiency and control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pastuerella multocida*, and *Histophilus somni* in groups of cattle fed in confinement for slaughter, where active BRD has been diagnosed in at least 10% of the animals in the group.

Additionally, data demonstrate that residues in food products derived from cattle treated with PULMOTIL 90 and RUMENSIN 90 will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

A valid veterinary feed directive (VFD) is required to dispense this drug. Any animal feed bearing or containing this drug will be fed to animals only by or on a lawful veterinary feed directive issued by a licensed veterinarian in the course of their professional practice. In addition, VFDs for tilmicosin phosphate are not refillable.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. The decision to restrict this drug to use by or on the order of a licensed veterinarian was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues. Because the drug will be administered in feed, the drug will be marketed as a VFD drug.

B. Exclusivity:

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

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.