Date of Approval: October 19, 2009

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 138-870

MGA plus RUMENSIN plus TYLAN

Melengestrol Acetate and Monensin and Tylosin Phosphate
Type A Medicated Articles to be Used in the Manufacture of Type C Medicated Feeds
Heifers Fed in Confinement for Slaughter

This supplement provides for an increase in the upper dose limit of monensin to 480 mg/hd/day based upon the December 1, 2006, approval (N-095735-C-0297) for monensin, and to update the name of the tylosin targeted bacteria to *Arcanobacterium pyogenes* based on the November 7, 2006, approval (N-012491-C-0318) for tylosin phosphate for increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), and prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in heifers fed in confinement for slaughter.

Sponsored by:
Pharmacia & Upjohn Co.,
a Division of Pfizer, Inc.

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I. GENERAL INFORMATION:

A. File Number: NADA 138-870

B. Sponsor: Pharmacia & Upjohn Co.,
a Division of Pfizer, Inc.
235 East 42d St.
New York, NY 10017

Drug Labeler Code: 000009

C. Proprietary Names: MGA plus RUMENSIN plus TYLAN

D. Established Names: Melengestrol acetate and monensin and tylosin phosphate

E. Pharmacological Categories: Melengestrol acetate: steroid hormone

Monensin: ionophore/anticoccidial

Tylosin phosphate: antimicrobial

F. Dosage Form: Type A medicated articles to be used in the manufacture of Type C medicated feeds

G. Amount of Active Ingredients: Melengestrol acetate: 200 and 500 g/lb

Monensin: 80 g/lb

Tylosin phosphate: 40 and 100 g/lb

H. How Supplied: Melengestrol acetate: 50 lb bag (dry), 40 lb container (liquid)

Monensin: 50 lb bag

Tylosin phosphate: 50 lb bag

I. How Dispensed: OTC

J. Dosage: Melengestrol acetate is added to the diet of heifers at 0.5 to 2.0 pounds per head per day of medicated feed containing 0.125 to 1.0 mg melengestrol acetate per pound to provide 0.25 to 0.5 mg melengestrol acetate per head per day.

Monensin is added to feedlot cattle diets at

concentrations of 10 to 40 g of monensin per ton of complete feed at a rate of 0.14 to 0.42 mg monensin per pound of body weight depending on severity of coccidiosis challenge up to 480 mg per head per day.

Tylosin is added to the cattle diets at concentrations of 8 to 10 g of tylosin phosphate per ton of complete feed to provide 60 to 90 mg tylosin per head per day.

K. Route of Administration: Oral, in feed

L. Species/Class: Heifers fed in confinement for slaughter

M. Indications: For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*, reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* in heifers fed in confinement for slaughter.

N. Effects of Supplement: This supplement provides for an increase in the upper dose limit of monensin to 480 mg/hd/day based upon the December 1, 2006, approval (N-095735-C-0297) for monensin, and to update the name of the tylosin targeted bacteria to *Arcanobacterium pyogenes* based on the November 7, 2006, approval (N-012491-C-0318) for tylosin phosphate, for increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), and prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in heifers fed in confinement for slaughter.

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.

Melengestrol acetate, as provided by Pharmacia & Upjohn Co., a Division of Pfizer, Inc., has previously been separately approved for use in feed for heifers fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) (21 CFR 558.342(e)(i)). Monensin, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in feed for feedlot cattle at the rate of 10 to 40 g/ton for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* (21 CFR 558.355(f)(3)(vii)). Tylosin phosphate, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in feed for beef cattle for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* (21 CFR 558.625(f)(1)(i)). Effectiveness of each drug, melengestrol acetate, monensin, and tylosin phosphate when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADAs 095-735 and 012-491 for monensin and tylosin phosphate, respectively, to which Pharmacia & Upjohn Co., a Division of Pfizer, Inc. has right of reference, and in Pharmacia & Upjohn Co., a Division of Pfizer, Inc.'s approved NADA 039-402 for melengestrol acetate.

Because melengestrol acetate, monensin, and tylosin phosphate each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that melengestrol acetate plus monensin plus tylosin phosphate provide appropriate concurrent use for the intended target population. The use of melengestrol acetate plus monensin plus tylosin phosphate provides appropriate concurrent use because these drugs are intended to treat different conditions [increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) for melengestrol acetate, prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* for monensin, and reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* for tylosin phosphate] likely to occur simultaneously with sufficient frequency in heifers 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.

Melengestrol acetate, as provided by Pharmacia & Upjohn, a division of Pfizer, Inc., has previously been separately approved for use in feed for heifers fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and supression of estrus (heat) (21 CFR 558.342(e)(i)). Monensin, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in feed for feedlot cattle at the rate of 10 to 40 g/ton for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* (21 CFR 558.355(f)(3)(vii)). Tylosin phosphate, as provided by Elanco Animal Health, A Division of Eli Lilly & Co., has previously been separately approved for use in feed for beef cattle for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* (21 CFR 558.625(f)(1)(i)).

Under the provisions of ADAA, this supplemental approval allows for the combination of melengestrol acetate (as provided by Pharmacia & Upjohn Co., a Division of Pfizer, Inc.), monensin (as provided by Elanco Animal Health, a Division of Eli Lilly & Co.), and tylosin phosphate (as provided by Elanco Animal Health a Division of Eli Lilly & Co.). Target animal safety for each drug, melengestrol acetate, monensin, and tylosin phosphate 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 095-735 and 012-491 for monensin and tylosin phosphate, respectively, to which Pharmacia & Upjohn, a Division of Pfizer, Inc. has right of reference, and in Pharmacia & Upjohn, a Division of Pfizer Inc.'s approved NADA 039-402 for melengestrol acetate. The Agency has found no substantiated scientific issue relating to the target animal safety of melengestrol acetate, monensin, and tylosin phosphate 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:

CVM did not require toxicology studies for this supplemental approval. Safety of the individual drugs in this combination product has been established by data in NADA 095-735 for monensin (FR 58289-58290, Vol:40, No. 242, December 16, 1975), NADA 039-402 (FOI Summary dated June 29, 1994) for melengestrol acetate, and NADA 012-491 (26 FR 4369, May 19, 1961) for tylosin phosphate.

B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. NADA 095-735 (FR 58289-58290, Vol:40, No. 242, December 16, 1975) contains a summary of the residue chemistry studies for monensin. NADA 039-402 (FOI Summary dated June 29, 1994), NADA 012-491 (26 FR 4369, May 19, 1961) and NADA 141-233 (FOI Summary dated September 11, 2007) contain a summary of the residue chemistry studies for melengestrol acetate and tylosin phosphate in cattle.

C. Microbial Food Safety:

The Agency determined that an assessment of microbial food safety associated with this combination of melengestrol acetate, monensin and tylosin phosphate approvable pursuant to the provisions of the Animal Drug Availability Act (1996), was not necessary at this time.

D. Analytical Method for Residues:

1. Analytical Method

The approval of NADA 095-735 for monensin (FR 58289-58290, Vol:40, No. 242, December 16, 1975), NADA 039-402 (FR 4241, Vol:59, No. 154, August 11, 1994) for melengestrol acetate and NADA 012-491 (26 FR 4369,

May 19, 1961) for tylosin phosphate contain the analytical method summaries for monensin, melengestrol acetate and tylosin phosphate in cattle.

2. Availability of Method

Analytical methods for detection of residues of monensin, melengestrol acetate and tylosin phosphate in cattle are available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The product labeling contains no user safety warnings for humans handling, administering, or exposed to the Type C medicated feed.

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 MGA plus RUMESIN plus TYLAN demonstrate that, when they used according to the label, they are safe and effective for increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii,* and reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* in heifers fed in confinement for slaughter. Additionally, data demonstrate that residues in food products derived from heifers fed in confinement for slaughter treated with MGA plus RUMENSIN plus TYLAN 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)(2)).

D. Patent Information:

No patents were submitted with this application.

VII. ATTACHMENTS:

Facsimile Labeling:
Melengestrol Acetate, Monensin and Tylosin Phosphate Type C Medicated Cattle Feed
Melengestrol Acetate, Monensin and Tylosin Phosphate Liquid Type C Medicated Cattle Feed