Approval Date: February 26, 2002

FREEDOM OF INFORMATION SUMMARY

NADA 138-870 C-0020, NADA 138-792 C-0021

Melengestrol Acetate (MGA®) plus Monensin Sodium (Rumensin®) plus Tylosin Phosphate (Tylan®)

Sponsored by :

Pharmacia & Upjohn Company

7000 Portage Road

Kalmazoo, MI 49001

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I. GENERAL INFORMATION

NADA Numbers: 138-870, 138-792

Sponsor: Pharmacia & Upjohn Company
7000 Portage Road
Kalmazoo, MI 49001

Established Names: Melengestrol acetate, monensin sodium, tylosin phosphate

Trade Names: MGA®, Rumensin®, and Tylan®

Marketing Status: OTC

Effect of the Supplement:

21 CFR 558.342(d)(5) currently provides for the combination use of melengestrol acetate, monensin and tylosin to provide 0.25 to 0.5 mg/hd/day melengestrol acetate, 50 to 360 mg/hd/day monensin and 90 mg/hd/day tylosin for heifers being fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, suppression of estrus (heat) and reduced incidence of liver abscesses.

These supplements provide for the treatment of the approved combination of melengestrol acetate, monensin and tylosin to be treated as a combination under the provisions of the Animal Drug Availability Act of 1996, and its reference to feed delivered drug combinations. The effect is to provide for the addition of the coccidiosis claim for monensin (0.14 to 0.42 mg/lb body weight depending on the severity of the challenge, up to 360 mg/hd/day) and the addition of the complete tylosin dose range (60 to 90 mg/hd/day) to this combination with melengestrol acetate for heifers being fed in confinement for slaughter.

II. INDICATIONS FOR USE

Increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), reduced incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes,* and the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in heifers being fed in confinement for slaughter.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

A. Dosage Form

MGA® is supplied as a Type A medicated article at the concentrations of 200 or 500 mg of melengesterol acetate activity per pound. Rumensin® is supplied as a Type A medicated article at a concentrations of 20, 30, 40, 60 or 80 grams of monensin activity per pound of premix. Tylan® is supplied as a Type A mediated article at the concentrations of 10, 40 or 100 grams of tylosin activity per pound of premix. MGA®, monensin, and tylosin may also be combined in a liquid Type B or C Medicated feed.

B. Route of Administration

Oral, via the feed

C. Recommended Dosage

(A) Add 0.5 to 2.0 pounds per head per day of a liquid or dry medicated feed containing 0.125 to 1.0 milligram of melengestrol acetate per pound to a medicated feed containing 10 to 30 grams of monensin and 8 to 10 grams of tylosin per ton to provide 0.25 to 0.5 mg/hd/day of melengestrol acetate, 0.14 to 0.42 mg monensin/lb body weight, depending on the severity of the challenge up to 360 mg/hd/day, and 60 to 90 mg/hd/day tylosin, or

(B) Add 0.5 to 2.0 pounds per head per day of a liquid or dry medicated feed containing 0.125 to 1.0 milligram of melengestrol acetate plus 25 to 720 milligrams of monensin per pound to 4.5 to 18 pounds of a dry medicated feed containing 10 to 40 grams of tylosin per ton to provide 0.25 to 0.5 mg/hd/day of melengestrol acetate, 0.14 to 0.42 mg monensin/lb body weight, depending on the severity of the coccidiosis challenge up to 360 mg/hd/day, and 60 to 90 mg/hd/day tylosin, or

(C) Add 0.5 to 2.0 pounds per head per day of a liquid or dry medicated feed containing 0.125 to 1.0 milligram melengestrol acetate (from a dry Type A article) 25 to 600 milligrams of monensin, and 45 to 180 milligrams of tylosin per pound to a ration of nonmedicated feed to provide 0.25 to 0.5 mg/hd/day of melengestrol acetate, 0.14 to 0.42 mg monensin/lb body weight, depending on the severity of the challenge up to 360 mg/hd/day, and 60 to 90 mg/hd/day tylosin.

IV. EFFECTIVENESS

In accordance with the Federal Food Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs 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, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to demonstrate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) each of the active ingredients or animal drugs intended for at least one use that is different from all the other active ingredients or animal drugs used in combination provides appropriate concurrent use for the intended target population, or 3) 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 animals drugs makes a contribution to the labeled effectiveness (21 USC §512(d)(4)(D)).

Melengestrol acetate, as provided by Pharmacia & Upjohn Company, has been previously separately approved for use in heifers in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) [21CFR558.342(d)(1)]. Monensin, as provided by Elanco Animal Health, has previously been separately approved for use in cattle being fed in confinement for slaughter for the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* [21 CFR 558.355(f)(3)(vii)]. Tylosin, as provided by Elanco Animal Health, has been previously separately approved for use in cattle being fed in confinement for slaughter for reduction of incidence in liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes* [21 CFR558.625(f)(1)(i). Under the provisions of ADAA, these supplements allow for the addition of the coccidiosis claim for monensin (0.14 to 0.42 mg/lb body weight depending on the severity of the challenge, up to 360 mg/hd/day) and the addition of the complete tylosin dose range (60 to 90 mg/hd/day) to these

combinations with melengestrol acetate for heifers being fed in confinement for slaughter. Effectiveness of each drug, melengestrol acetate, monensin, and tylosin when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Pharmacia & Upjohn's NADA 39-402 and 34-254, and Elanco Animal Health's NADAs 95-735 and 12-491, respectively.

Melenegestrol acetate, monensin and tylosin are each intended for a different use than the other drugs in the combination and therefore the NADA need not demonstrate, by substantial evidence, that each contributes to the labeled effectiveness of the combination. Melengestrol acetate, monensin and tylosin provide appropriate concurrent use because these drugs are intended to treat different conditions likely to occur simultaneously with sufficient frequency in heifers fed in confinement for slaughter (Melengestrol acetate, the suppression of estrus (heat); monensin, coccidioisis; tylosin, reduced incidence of liver abscesses). There is no more than one nontopical antibacterial (tylosin) contained in these combinations intended for use in Type B and Type C feeds. Monensin is not considered to be an antibacterial animal drug for use in cattle fed in confinement for slaughter for the purposes of 512(d)(4) of the FFDCA, because monensin is classified as an ionophore.

V. ANIMAL SAFETY

In accordance with the Federal Food Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA 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 or a scientific issue raised by target animal observations contained in studies submitted to the NADA for the combination and the FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

Melengestrol acetate, as provided by Pharmacia & Upjohn Company, has been previously separately approved for use in heifers in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and the suppression of estrus (heat) [21CFR558.342(d)(1)]. Monensin, as provided by Elanco Animal Health, has previously been separately approved for use in cattle being fed in confinement for slaughter for the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* [21 CFR 558.355(f)(3)(vii)]. Tylosin, as provided by Elanco Animal Health, has been previously separately approved for use in cattle being fed in confinement for slaughter for reduction of incidence in liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes* [21 CFR558.625(f)(1)(i). Under the

provisions of ADAA, these supplements allow for the addition of the coccidiosis claim for monensin (0.14 to 0.42 mg/lb body weight depending on the severity of the challenge, up to 360 mg/hd/day) and the addition of the complete tylosin dose range (60 to 90 mg/hd/day) to these combinations with melengestrol acetate for heifers being fed in confinement for slaughter. Target animal safety of each drug, melengestrol acetate, monensin, and tylosin when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Pharmacia & Upjohn's NADA 39-402 and 34-254, and Elanco Animal Health's NADAs 95-735 and 12-491, respectively.

The Agency has not found any substantial scientific issues relating to the target animal safety of melengestrol acetate, monensin and tylosin when used in combination under these NADAs and no scientific issues have been raised by target animal observations submitted as a part of these NADAs for these combinations. Thus pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety study(ies) are required for the supplemental approvals of NADAs 138-870 and 138-792.

VI. HUMAN SAFETY

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients of animal drugs intended for use in combination have been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal time for the respective active ingredients or animal drugs exceeds the established tolerances, or one or more of the active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or animal drug in the combination. Safety of this combination product has been established by data in NADA 12-491 for tylosin, NADA 95-735 for monensin, NADA 39-402 and 34-254 for melengestrol acetate, and the original FOI for NADA 138-870 and 138-792 (melengestrol acetate, monensin and tylosin).

For melengestrol acetate, a tolerance of 25 ppb is established for residues of the parent compound, in fat of cattle as codified under 21 CFR 556.380.

For monensin, a tolerance of 0.05 ppm is established for negligible residues of monensin in the edible tissues of cattle and goats as codified under 21 CFR 556.420.

For tylosin, a tolerance of 0.2 ppm is established for negligible residue of tylosin in uncooked fat, muscle, liver, and kidney in cattle as codified under 21 CFR 556.740.

D. Withdrawal Time

There is a 0 day withdrawal for MGA®, Rumensin®, and Tylan®. Refer to the approved NADAs (NADA 39-402 and 34-254, 95-735, and 12-491, respectively). Tissue residue non-interference was adequately shown, therefore the combination qualifies for a zero withdrawal period.

E. Regulatory Method

Regulatory methods are available at the Center for Veterinary Medicine/FDA, HFV-199, 7500 Standish Place, Rockville, MD 20855.

F. User Safety Concern

Refer to the MSDS's for melengestrol acetate, tylosin and monensin (NADAs 39-402 and 34-254, 12-491, and 95-735, respectively) by contacting the manufacturer for the MSDS.

VII. AGENCY CONCLUSIONS

The data submitted in support of these NADAs 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 melengestrol acetate (to provide 0.25 to 0.50 mg/head/day) plus monensin (to provide 0.14 to 0.42 mg/lb body weight depending upon the severity of the challenge, up to 360 mg monensin/head/day) plus tylosin (to provide 60-90 mg/head/day) is safe and effective for increased rate of weight gain, improved feed efficiency; suppression of estrus (heat); reduced incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes;* and prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in heifers being fed in confinement for slaughter.

Pursuant to 21 CFR 514.106(b)(2)(vi), these combination NADA approvals are regarded as a Category II supplemental change which did not require a reevaluation of the safety and effectiveness data in the parent NADAs.

Under section 512(c)(2)(F)(iii) of the FFDCA, these approvals for food producing animals do not qualify for marketing exclusivity because the supplemental applications do not contain substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than

bioequivalence or residue studies) required for the approval and conducted or sponsored by the applicant.

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 retain its over-the-counter marketing status.

VIII. APPROVED PRODUCT LABELING

A copy of the draft facsimile labeling is attached to this document.

A. Blue Bird Label - Liquid Type C Medicated Cattle Feed M-R-T+

B. Blue Bird Label - Type C Medicated Cattle Feed M-R-T+