Approval Date: February 26, 2002

FREEDOM OF INFORMATION SUMMARY

NADA 124-309, 125-476

Melengestrol Acetate (MGA®) plus Monensin Sodium (Rumensin®)

Sponsored by :

Pharmacia & Upjohn Company

7000 Portage Road

Kalmazoo, MI 49001

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I. GENERAL INFORMATION

NADA Numbers: 124-309, 125-476

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

Established Names: Melengestrol acetate and monensin sodium

Trade Names: MGA® and Rumensin®

Marketing Status: OTC

Effect of the Supplement:

21 CFR 558.342(d)(2) currently provides for the combination use of melengestrol acetate and monensin to provide 0.25 to 0.4 mg/hd/day of melengestrol acetate and 50 to 360 mg/hd/day monensin for heifers being fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency and suppression of estrus (heat).

These supplements provide for the treatment of the approved combination of melengestrol acetate and monensin 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. This effect is to provide for the addition of the claim for prevention and control of coccidiosis on a mg/lb body weight basis for monensin to this combination with melengestrol acetate for Type B and Type C medicated feeds for heifers being fed in confinement for slaughter.

II. INDICATIONS FOR USE

Increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), 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 100, 200 or 500 mg of melengestrol acetate activity per pound. Rumensin® is supplied as a Type A medicated article at a concentration of 20, 30, 45, 60, 80, or 90.7 grams of monensin activity per pound of premix. Melengestrol acetate and monensin may also be combined in a liquid Type C Medicated feed.

B. Route of Administration

Oral, via the feed

C. Recommended Dosage

A. Feed to heifers at a rate of 0.5 to 2.0 pounds per head per day a feed containing 0.125 to 0.80 mg melengestrol acetate to provide 0.25 to 0.4 mg melengestrol acetate and 25 to 720 mg of monensin to provide 0.14 to 0.42 mg/lb body weight, depending on the severity of the challenge, up to 360 mg monensin per head per day. This liquid Type C product must be top-dressed onto or mixed into a complete feed prior to feeding, or

B. Add at the rate of 0.5 to 2.0 pounds per head per day a medicated feed (liquid or dry) containing 0.125 to 0.80 milligram of melengestrol acetate per pound to a feed containing 10 to 30 grams of monensin per ton to provide 0.14 to 0.42 mg/lb body weight, depending on the severity of the challenge, up to 360 mg monensin per head per day.

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 previously been separately approved for use in heifers being fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and the suppression of estrus (heat) [21 CFR 558.342(d)(1)(i)]. 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)]. Under the provisions of ADAA, these supplements allow for the addition of the coccidiosis claim for monensin as provided by Elanco Animal Health and approved separately for use in confined cattle for the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* (0.14 to 0.42 mg/lb body weight per day up to 360 mg depending on the severity of the challenge). Effectiveness of each drug, melengestrol acetate and monensin, 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 NADA 95-735, respectively.

Monensin is intended for a different use than melengestrol acetate and therefore the NADAs need not demonstrate, by substantial evidence, that monensin contributes to the labeled effectiveness of the combination. Melengestrol acetate and monensin provide appropriate concurrent use because these drugs are intended to treat different conditions (melengestrol acetate: heat suppression, monensin: prevention and control of coccidiosis) likely to occur simultaneously with sufficient frequency in heifers being fed in confinement for slaughter. There is no

more than one nontopical antibacterial contained in these combination animal drugs intended for use in Type B and Type C medicated feeds.

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 previously been separately approved for use in heifers being fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and the suppression of estrus (heat) [21 CFR 558.342(d)(1)(i)]. 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)]. Under the provisions of ADAA, these supplements allow for the addition of the coccidiosis claim for monensin as provided by Elanco Animal Health and approved separately for use in confined cattle for the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* (0.14 to 0.42 mg/lb body weight per day up to 360 mg depending on the severity of the challenge). Target animal safety of each drug, melengestrol acetate and monensin, 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 NADA 95-735, respectively.

The Agency has not found any substantial scientific issues relating to the target animal safety of melengestrol acetate or monensin when used in combination under these NADAs and no scientific issues has 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 NADA 124-309 and 125-476.

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 95-735 for monensin, NADA 39-402 and 34-254 for melengestrol acetate, and the original FOI for NADA 124-309 and 125-476 (MGA and monensin).

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.

A. Withdrawal Time

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

B. Regulatory Method

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

C. User Safety Concern

Refer to the MSDS's for melengestrol acetate and monensin (NADAs 39-402 and 34-254, 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 0.4 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) is safe and effective for increased rate of weight gain, improved feed efficiency; suppression of estrus (heat); 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+
B. Blue Bird Label - Type C Medicated Cattle Feed M-R+