

HEA 305

Approval Date: FEB 26 2002

FREEDOM OF INFORMATION SUMMARY

NADA 139-192 C-0020, NADA 138-995 C-0017

Melengestrol Acetate (MGA®) plus Tylosin Phosphate (Tylan®)

Sponsored by :

Pharmacia & Upjohn Company

7000 Portage Road

Kalamazoo, MI 49001

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I. GENERAL INFORMATION

NADA Numbers: 139-192, 138-995

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

Established Names: Melengestrol acetate and tylosin phosphate

Trade Names: MGA® and Tylan®

Marketing Status: OTC

Effect of Supplement:

21 CFR 558.342(d)(4) currently provides for the combination use of melengestrol acetate and tylosin to provide 0.25 to 0.5 mg/hd/day of melengestrol acetate 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 provides for the treatment of the approved combination of melengestrol acetate plus 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 complete tylosin dose range to this combination (60 to 90 mg/hd/day tylosin) with melengestrol acetate for Type B and Type C medicated feeds 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 caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*.

II. INDICATIONS FOR USE

For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat) and reduced incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*.

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. 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. Tylan and MGA 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 8 to 10 grams of tylosin per ton to provide 0.25 to 0.50 mg/hd/day of melengestrol acetate and 60 to 90 mg/hd/day of 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 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 0.50 mg/hd/day of melengestrol acetate and 60 to 90 mg/hd/day of 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 of melengestrol acetate plus 45 to 180 milligrams of tylosin per pound to a ration of nonmedicated feed to provide 0.25 to 0.50 mg/hd/day of melengestrol acetate and 60 to 90 mg/hd/day of 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 previously been separately approved for use in heifers fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) [21 CFR 558.342 (d)(1)(i)]. Tylosin, as provided by Elanco Animal Health, has previously been separately approved for use in cattle fed in confinement for slaughter for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes* [21 CFR 558.625 (f)(1)(i)]. Under the provisions of ADAA, these supplements allow for the addition of the complete tylosin dose range (60 to 90 mg/hd/day tylosin) as provided by Elanco Animal Health, and approved separately for use in cattle for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*. Effectiveness for each drug, melengestrol acetate 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 NADA 12-491, and respectively.

Tylosin is intended for a different use than melengestrol acetate, therefore the NADA need not demonstrate, by substantial evidence, that tylosin contributes to the labeled effectiveness of the combinations. Melengestrol acetate and tylosin provide appropriate concurrent use because these drugs are intended to treat different conditions (melengestrol acetate; heat suppression, tylosin; liver abscesses) likely to occur simultaneously with sufficient frequency in heifers 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 fed in confinement for slaughter for improved feed efficiency, increased rate of weight gain, and suppression of estrus (heat) [21 CFR 558.342 (d)(1)(I)]. Tylosin, as provided by Elanco Animal Health, has previously been separately approved for use in cattle fed in confinement for slaughter for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes* [21 CFR 558.625 (f)(i)(a)]. Under the provisions of ADAA, these supplements allow for the addition of the complete tylosin dose range (60 to 90 mg/hd/day tylosin) as provided by Elanco Animal Health, and approved separately for use in cattle for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*. Target animal safety for each drug, melengestrol acetate and tylosin, when administered alone in accordance with its approved uses and conditions of use, are demonstrated in Pharmacia & Upjohn's NADA 39-402 and 34-254, and Elanco Animal Health's NADA 12-491 respectively.

The Agency has not found any substantial scientific issues relating to the target animal safety of melengestrol acetate or 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 these supplemental approvals of NADA 139-192 and 138-995.

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 NADA 39-402 and 34-254 for melengestrol acetate, 12-491 for tylosin and the original FOI for NADAs 139-192 and 138-995 (MGA® and Tylan® combination).

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

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® and Tylan®. Refer to the approved NADAs 39-402 and 34-254 and NADA 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 and tylosin phosphate (NADAs 39-402 and 34-254 and NADA 12-491, 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 0.5 mg/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); and reduced incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*.

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. Type B BLUEBIRD LABEL FOR MGA® and TYLAN®

Net Weight on Bulk Invoice

**Liquid Type C Medicated Cattle Feed M-T+
Do Not Feed Undiluted
For Use in Heifer Feeds Only**

Indications

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 caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*.

Active Drug Ingredients

Melengestrol acetate (MGA[®])..... 0.0000276 to 0.00022% (0.25 to 2 g/ton)*
Tylosin phosphate (Tylan[®])..... 90 to 360 g/ton*

Guaranteed Analysis

Crude Protein, not less than.....	_____	%
Non-Protein Nitrogen (NPN) ¹ , not more than	_____	%
Crude Fat, not less than.....	_____	%
Crude Fiber, not more than.....	_____	%
Calcium, not less than.....	_____	%
Calcium, not more than.....	_____	%
Phosphorus, not less than.....	_____	%
Salt ² , not less than.....	_____	%
Salt ² , not more than.....	_____	%
Sodium ³ , not less than.....	_____	%
Sodium ³ , not more than.....	_____	%
Potassium, not less than.....	_____	%
Vitamin A ^{2,4} , not less than.....	_____	I.U./lb
Dry Matter, not less than.....	60	%
Dry Matter, not more than.....	75	%
pH.....	4.5 to 6.0	

¹When added.

²If added.

³Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

⁴Other than precursors of Vitamin A.

Ingredients

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

* Final printed label on formulated Type C medicated feed must bear a single concentration of each drug.

Feeding Directions

When preparing a liquid Type C feed, tylosin must be pre-solubilized in 50% urea for approximately 1 hour prior to the inclusion of any additional feed components or active ingredients. Maintain the pH between 4.5 and 6.0.

For stored liquid Type C medicated feeds containing melengestrol acetate and tylosin, recirculate or agitate liquid Type C medicated feeds daily even when no Type C feed is used and immediately prior to use for no less than 10 minutes moving not less than 1% of the tank contents per minute from the bottom to the top of the tank.

Each pound contains 0.125 to 1.0 mg melengestrol acetate and 45 to 180 mg of tylosin. Feed to heifers at a rate of 0.5 to 2.0 pounds per head per day to provide 0.25 to 0.5 mg melengestrol acetate and 60 to 90 mg tylosin per head per day. Prior to feeding, this Liquid Type C product must be top-dressed onto a complete feed or mixed into the amount of complete feed consumed by an animal per day.

Caution

Feed continuously as sole ration.

MGA is for use only in heifers being fed in confinement for slaughter. Not effective in steers and spayed heifers.

When mixing and handling Tylan®, use protective clothing, impervious gloves and a dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water.

Manufactured by

Blue Bird Feed Company
Anytown, IN 11111

Expiration Date: (8 weeks after manufacture)

MGA® is a trademark of Pharmacia & Upjohn Company
Tylan® is a trademark of Eli Lilly and Company.

Net Weight on Bulk Invoice

Type C Medicated Cattle Feed M-T+
Do Not Feed Undiluted
For Use in Heifer Feeds Only

Indications

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 caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*.

Active Drug Ingredients

Melengestrol acetate (MGA[®])..... 0.0000276 to 0.00022% (0.25 to 2 g/ton)*
Tylosin phosphate (Tylan[®])..... 90 to 360 g/ton*

Guaranteed Analysis

Crude Protein, not less than.....	_____ %
Non-Protein Nitrogen (NPN) ¹ , not more than	_____ %
Crude Fat, not less than.....	_____ %
Crude Fiber, not more than.....	_____ %
Calcium, not less than.....	_____ %
Calcium, not more than.....	_____ %
Phosphorus, not less than.....	_____ %
Salt ² , not less than.....	_____ %
Salt ² , not more than.....	_____ %
Sodium ³ , not less than.....	_____ %
Sodium ³ , not more than.....	_____ %
Potassium, not less than.....	_____ %
Vitamin A ^{2, 4} , not less than.....	_____ I.U./lb

¹When added.

²If added.

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⁴Other than precursors of Vitamin A.

Ingredients

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* Final printed label on formulated Type C medicated feed must bear a single concentration of each drug.

Feeding Directions

Each pound contains 0.125 to 1.0 mg melengestrol acetate and 45 to 180 mg of tylosin. Feed to heifers at a rate of 0.5 to 2.0 pounds per head per day to provide 0.25 to 0.5 mg melengestrol acetate and 60 to 90 mg tylosin per head per day. Prior to feeding, this Type C product must be top-dressed onto a complete feed or mixed into the amount of complete feed consumed by an animal per day.

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