

Date of Approval: SEP 19 2005

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-375

HEIFERMAX 500 (melengestrol acetate) plus RUMENSIN
(monensin sodium) and TYLAN (tylosin phosphate)

Type A Medicated Articles

Indication for use: 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 the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in heifers being fed in confinement for slaughter.

Sponsored by:
Ivy Laboratories,
Div. of Ivy Animal Health, Inc.

2005-200-375

FOIS 1

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. File Number: ANADA 200-375
- b. Sponsor: Ivy Laboratories,
Div. of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214

Drug Labeler Code: 021641
- c. Established Names: Melengestrol acetate, monensin sodium,
tylosin phosphate
- d. Proprietary Names: HEIFERMAX 500, RUMENSIN, TYLAN
- e. Dosage Form: Type A medicated articles for use in
combination for the manufacture of three-
way Type C medicated feeds
- f. How Supplied: HEIFERMAX 500 – liquid premix
RUMENSIN – dry granulated premix
TYLAN – dry premix
- g. How Dispensed: OTC
- h. Amount of Active Ingredients: HEIFERMAX 500: 500 mg of
melengestrol acetate activity per pound of
premix

RUMENSIN: 20, 30, 40, 60 or 80 grams of
monensin sodium activity per pound of
premix

TYLAN: 10, 40 or 100 grams of tylosin
phosphate activity per pound of premix
- i. Route of Administration: Orally in feed
- j. Species/Class: Beef cattle; heifers fed in confinement for
slaughter

- k. Recommended Dosage: Feed to heifers at a rate of 0.5 to 2.0 pounds Type C medicated feed per day to provide 0.25 to 0.5 mg melengestrol acetate per head per day in combination with 50 to 360 mg monensin per head per day, and 60 to 90 mg tylosin per head per day.
- l. Pharmacological Category: Hormone/Anticoccidial/Antimicrobial
- m. Indications: 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 the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* in heifers being fed in confinement for slaughter.
- n. Generic Product: HEIFERMAX 500; melengestrol acetate; ANADA 200-343; Ivy Laboratories, a Div. of Ivy Animal Health, Inc.
- o. Pioneer Product/Listed Product: MGA 500; melengestrol acetate; NADA 034-254; Pharmacia & Upjohn Co., a Division of Pfizer, Inc.
- RUMENSIN, monensin sodium, NADA 095-735; Elanco Animal Health, A Division of Eli Lilly & Co.
- TYLAN; tylosin phosphate; NADA 012-491; Elanco Animal Health, A Division of Eli Lilly & Co.
- MGA plus RUMENSIN plus TYLAN; melengestrol acetate, monensin sodium, tylosin phosphate; NADA 138-870; Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

2. TARGET ANIMAL SAFETY AND EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Ordinarily, the ANADA sponsor shows the generic product is bioequivalent to the pioneer, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from the requirement of an *in vivo* bioequivalence study. (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guidance, revised October 9, 2002).

This approval is for the use of HEIFERMAX 500 (melengestrol acetate) in combination with RUMENSIN (monensin sodium) and TYLAN (tylosin phosphate) for the manufacture of three-way Type C medicated feeds. This combination feed use product is a generic copy of MGA 500 (melengestrol) in combination with RUMENSIN and TYLAN, NADA 138-870, sponsored by Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

According to CVM's fourth policy letter issued on November 2, 1989, with regard to the implementation of GADPTRA, after the approval of an ANADA for a generic Type A medicated article, the generic sponsor is entitled to approval for all the feed-mixed combinations for which the pioneer is approved. Bioequivalence and tissue residue studies are not required for the approval of the generic feed use combinations (Type B or C medicated feeds). Melengestrol is codified under 21 CFR 558.342. Monensin is codified under 21 CFR 558.355. Tylosin is codified under 21 CFR 558.625. The combination of melengestrol, monensin, and tylosin is codified under 21 CFR 558.342(d).

3. HUMAN SAFETY:

- **Tolerances for Residues:**

The tolerances established for the pioneer product apply to the generic product. A tolerance of 25 ppb is established for residues of the parent compound, melengestrol acetate, in fat of cattle under 21 CFR 556.380.

A tolerance of 0.05 ppm is established for negligible residues of monensin in the edible tissues of cattle as codified under 21 CFR 556.420.

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

- **Withdrawal Times:**
The withdrawal times for the pioneer product are those previously assigned to the pioneer product.

No withdrawal times are assigned.

- **Regulatory Method for Residues**
Withdrawal times are not assigned for any of the drug ingredients in this combination product. Therefore, regulatory methods for residues are not available.

4. AGENCY CONCLUSIONS:

This ANADA filed under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that the medicated feed use combination product HEIFERMAX 500, RUMENSIN, and TYLOSIN, when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as indicated below:

Generic Labeling for ANADA 200-375:

Blue Bird labeling for Type C medicated feeds

Pioneer Labeling for NADA 138-870:

Blue Bird labeling for Type C medicated feeds

Net Weight on Bulk Invoice

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

HeifermaX™ 500 plus Rumensin® plus Tylan®
ANADA 200-375, Approved by FDA

Indications

Heifers being fed in confinement for slaughter: 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 the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*.

Active Drug Ingredients

Melengestrol acetate (HeifermaX™ 500).....	0.0000276 to 0.00022% (0.25 to 2 g/ton)*
Monensin sodium (Rumensin®).....	50 to 1200 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 liquid feeds stored in recirculating tank systems: Recirculate immediately prior to use for not less than 10 minutes, moving not less than 1 percent of the tank contents per minute from the bottom of the tank to the top. Recirculate daily as described even when not used.

For liquid feeds stored in mechanical, air, or agitation-type tank systems: Agitate immediately prior to use for not less than 10 minutes, creating a turbulence at the bottom of the tank that is visible at the top. Agitate daily as described even when not used.

Each pound of feed contains 0.125 to 1.0 mg melengestrol acetate, 25 to 600 mg monensin, and 45 to 180 mg tylosin per pound. 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, 0.14 to 0.42 mg monensin/lb body weight, depending on the severity of the challenge, up to a maximum 360 mg/hd/day, 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.

Melengestrol is for use only in heifers being fed in confinement for slaughter. Not effective in steers or spayed heifers.

Inadequate mixing or agitation of Monensin Liquid Type C medicated feed has resulted in increased monensin concentration, which has been fatal to cattle. Do not allow horses or other equines access to feed containing monensin. Ingestion of monensin by horses has been fatal. Monensin medicated cattle feed is safe for use only in cattle. Consumption by unapproved species may result in toxic reactions. Feeding undiluted or mixing errors resulting in high concentrations of monensin has been fatal to cattle. Must be thoroughly mixed in feeds before use. Do not exceed the levels of monensin recommended in the feeding directions, as reduced-average daily gains may result.

When mixing and handling Monensin and Tylosin, 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.

Warning

A withdrawal time has not been established for pre-ruminating calves. Do not use in calves to be processed for veal.

Manufactured by

Blue Bird Feed Company
Anytown, IN 11111

Expiration Date: (8 weeks after manufacture)

HeifermaX™ is a trademark of Ivy Animal Health, Inc.
Rumensin® and Tylan® are trademarks of Eli Lilly and Company.

Net Weight on Bulk Invoice

Liquid Type C Medicated Cattle Feed M-R-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), 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*.

Active Drug Ingredients

Melengestrol acetate (MGA®).....	0.0000276 to 0.00022% (0.25 to 2 g/ton)*
Monensin sodium (Rumensin®).....	50 to 1200 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, monensin 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 of feed contains 0.125 to 1.0 mg melengestrol acetate, 25 to 600 mg monensin, and 45 to 180 mg tylosin per pound. 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, 0.14 to 0.42 mg monensin/lb body weight, depending on the severity of the challenge, up to a maximum 380 mg/hd/day, 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 or spayed heifers.

Inadequate mixing or agitation of Rumensin® Liquid Type C Medicated Feed has resulted in increased monensin concentration, which has been fatal to cattle. Do not allow horses or other equines access to formulations containing monensin. Ingestion of monensin by equines has been fatal. Monensin medicated cattle feed is safe for use only in cattle. Consumption by unapproved species may result in toxic reactions. Feeding undiluted or mixing errors resulting in high concentrations of monensin has been fatal to cattle. Must be thoroughly mixed in feeds before use. Do not exceed the levels of monensin recommended in the feeding directions, as reduced average daily gains may result.

When mixing and handling Rumensin® and 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.

Warning

Do not feed to lactating dairy cows. A withdrawal time has not been established for pre-ruminating calves. Do not use in calves to be processed for veal.

Manufactured by

Blue Bird Feed Company
Anytown, IN 11111

Expiration Date: (8 weeks after manufacture)

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