Approval Date: June 29, 1994

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 138-870

B. Sponsor

The Upjohn Company

C. Proprietary Name

MGA; 100/200 Premix, MGA; 500 Liquid Premix, RUMENSIN;, TYLAN

D. Established Name

melengestrol acetate, monensin, tylosin

E. Dosage Form

Feed

F. Dispensing Status

OTC

G. Dosage Regimen

Melengestrol acetate: 0.25 to 0.5 mg/head/day

Monensin (as monensin sodium):50 to 360 mg/head/day (5 to 30 g/ton air dried complete feed)

Tylosin (as tylosin phosphate):90 mg/head/day (8 to 10 g/ton air dried complete feed)

NOTES: Approval has been granted to feed 0.25 to 0.5 mg melengestrol acetate per head per day in combination with 90 mg tylosin per head per day with or without 50 to 360 mg monensin per head per day to heifers fed in confinement for slaughter. The supplement containing melengestrol acetate is fed at a rate of 0.5 to 2.0 pounds per head.

H. Route of Administration

Oral

I. Indication

This supplement does not affect the existing indications for the combined administration of melengestrol acetate and tylosin either with or without monensin which are:

For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat) and reduced incidence of liver abscesses in heifers fed in confinement for slaughter.

J. Effect of Supplement

This supplement provides for removal of the requirement of a pre-slaughter drug withdrawal period for heifers fed melengestrol acetate when melengestrol acetate is fed in combination with tylosin or with tylosin and monensin. Previous approvals have required a 48 hour pre-slaughter drug withdrawal for heifers fed melengestrol acetate when fed in combination with either tylosin or monensin and tylosin.

II. EFFECTIVENESS

This supplement does not affect the indications for these combinations.

III. TARGET ANIMAL SAFETY

This supplement does not affect target animal safety of these combinations.

IV. HUMAN FOOD SAFETY

A. Tolerance and Withdrawal Period.

As stated in the Freedom of Information Summary for the supplemental application for melengestrol acetate (NADA's 034-254 and 039-402), concurrently approved with this application, the tolerance of melengestrol acetate (MGA) is established as 25 ppb in edible tissue of treated animals and fat is designated as the target tissue for monitoring purposes. The approval also provides for the deletion of the 48-hour withdrawal period.

A tolerance of 0.05 ppm has been established for negligible residues of monensin in the edible tissues of cattle (21 CFR 556.420). No pre-slaughter withdrawal period is required for cattle fed monensin (21 CFR 558.355).

A tolerance of 0.2 ppm has been established for negligible residues of tylosin in the uncooked edible tissues of cattle (21 CFR 556.740). No pre-slaughter withdrawal period is required for cattle fed tylosin (21 CFR 558.625).

B. Residue Depletion Following Combination Feeding of Melengestrol Acetate, Monensin and Tylosin.

Data previously summarized in Freedom of Information Summaries for these NADA's, dated 30 April 1990, demonstrate that the concentration of melengestrol acetate in fat is below the tolerance of 25 ppb established by the approval of the supplemental application for MGA (NADA's 034-254 and 039-402) and that the concentration of monensin and tylosin in liver are below their tolerances, when heifers are fed melengestrol acetate, tylosin and monensin in combination, each at their highest approved dosage, and slaughtered without a pre-slaughter withdrawal. This study is summarized below.

Groups of heifers were individually fed for 90 days either no additive (control, n=14) or melengestrol acetate, monensin and tylosin in combination at 1X (n=7), 3X (n=7) or 5X (n=7) the highest approved dosage for each additive (1X = 0.5 mg melengestrol acetate, 30 g monensin/ton air dried feed and 10 g tylosin/ton air dried feed). The heifers were slaughtered at practical zero withdrawal.

Perirenal fat samples were collected from all heifers for analysis of melengestrol acetate residue using the method described in JAOAC 59:507-515:1976. This method has a limit of sensitivity of 10 ppb. All fat samples from heifers in the control and 1X treatment group had concentration of melengestrol acetate below 10 ppb. The average concentration of melengestrol acetate in fat samples from heifers in the 3X and 5X dose groups were 29.2 ppb (range 18.2 to 39.6 ppb) and 42.2 ppb (range 35.8 to 49 ppb), respectively.

Liver samples were collected from seven of the control heifers and from the seven heifers in the 1X treatment group for analysis of monensin and tylosin residues. No residues of either monensin or tylosin were detected in any of the liver samples from these heifers. The limit of detection for these analyses were 0.04 and 0.1 ppm for monensin and tylosin, respectively.

Conclusion

These data demonstrate that when heifers are slaughtered without a pre-slaughter withdrawal following feeding of melengestrol acetate, tylosin and monensin in combination the concentration of melengestrol acetate in fat is below the established tolerance for melengestrol acetate and the concentration of monensin and tylosin in liver are below their established tolerances.

C. Assay noninterference

Data, previously summarized in Freedom of Information Summaries for these NADA's, dated 30 April 1990, demonstrated

1. the presence of monensin and tylosin does not interfere with the tissue residue assay for melengestrol acetate;

2. presence of monensin and melengestrol acetate does not interfere with the tissue residue assay for tylosin; and

3. presence of melengestrol acetate and tylosin does not interfere with the tissue residue assay for monensin.

D. Regulatory methods

Practical regulatory methods for analysis of tissue residues of melengestrol acetate, monensin and tylosin may be found in the *Food Additives Analytical Manual* on display in FDA's Freedom of Information Public Room (Parklawn Building, Room 12A30).

E. Conclusions

This supplement provides for the deletion of the requirement for a 48 hour pre-slaughter withdrawal period for melengestrol acetate when fed in combination with tylosin and either with or without monensin. No changes are made in either the approved dosages of any of these additives, the approved indications of use or in the target class of livestock. The data submitted support the conclusion that the concentration of melengestrol acetate in fat is below the established tolerance for melengestrol acetate when heifers are slaughtered without a pre-slaughter withdrawal following the combined feeding of melengestrol acetate and tylosin either with or without monensin. Accordingly this change in regulations for melengestrol acetate is not expected to have adverse effects on public health or food safety.

V. AGENCY CONCLUSIONS

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the removal of the requirement for a 48 hour withdrawal period prior to slaughter for heifers fed melengestrol acetate when melengestrol acetate is fed in combination with tylosin or with tylosin and monensin. This supplement evoked a reevaluation of the toxicity data for MGA contained in NADA's 034-254 and 039-402.

Adequate data were submitted which permitted the Agency to conclude that a withdrawal period is not necessary for heifers fed these combinations.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food animals does not qualify for marketing exclusivity because the supplemental application did not contain new clinical or field investigations (other than bioequivalence or residue studies) and new human food safety studies (other than bioequivalence or residue studies) essential to the approval and conducted or sponsored by the applicant.

VI. ATTACHMENTS

1. Bag or bulk Medicated Heifer Dry Supplement (Type B Medicated Feed) containing MGA and tylosin

2. Bag or bulk Medicated Heifer Dry Supplement (Type B Medicated Feed) containing MGA, monesin and tylosin

Copies of these labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

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