Approval Date: June 29, 1994

I. GENERAL INFORMATION

A. File Number

NADA 138-992

B. Sponsor

The Upjohn Company
Agricultural Division
Kalamazoo, MI 49001

C. Proprietary Name

MGA® 100/200 Premix, MGA® 500 Liquid Premix, BOVATEC®, TYLAN®

D. Established Name

Melengestrol acetate, Lasalocid, Tylosin

E. Dosage Form

Feed

F. Dispensing Status

OTC

G. Recommended Dosages:

Melengestrol acetate: 0.25 to 0.5 mg/head/day
Lasalocid (as lasalocid sodium): 100 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 100 to 360 mg lasalocid per head per day either with or without 90 mg tylosin 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 these combinations which are:

- The feeding of melengestrol acetate and lasalocid in combination is indicated for increased rate of weight gain, improved feed efficiency and suppression of estrus (heat) in heifers fed in confinement for slaughter.
- The feeding of melengestrol acetate, lasalocid and tylosin in combination is indicated 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 either with lasalocid or with lasalocid and tylosin.

II. EFFECTIVENESS

This supplement does not affect the efficacy of these combinations.

III. TARGET ANIMAL SAFETY

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

IV. HUMAN FOOD SAFETY

A. Tolerance and withdrawal period.

Melengestrol acetate
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.
Lasalocid
In cattle parent lasalocid has been established as the marker residue for total lasalocid sodium residues, liver was selected as the target tissue and 0.7 ppm for parent lasalocid in liver was established as the tolerance (21 CFR 556.347). No pre-slaughter withdrawal period is required for cattle fed lasalocid (21 CFR 558.311).
Tylosin
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, lasalocid and tylosin.

Data previously summarized in Freedom of Information Summaries for NADA's 138-904 and 138-992, dated 30 April 1990; and NADA's 139-876 and 140-288, dated 16 December 1987; 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 lasalocid and tylosin in liver are below their tolerances when heifers are fed melengestrol acetate, lasalocid and tylosin in combination, each at their highest approved dosage, and slaughtered without a pre-slaughter drug withdrawal. This study is summarized below:

- Groups of heifers were fed for 90 days either no additive (control, n=14) or melengestrol acetate, lasalocid and tylosin in combination at 1X (n=7), 3X (n=7) or 5X (n=7) the highest approved dosage for each additive (lX = 0.5

mg melengestrol acetate, 30 g lasalocid/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 official AOAC method (JAOAC 59:507-515:1976). This method has a limit of sensitivity of 10 ppb. All fat samples from the control heifers and 5 of 7 heifers in the 1X treatment group had concentration of melengestrol acetate below 10 ppb. Fat samples from the remaining two heifers in the 1X group contained melengestrol acetate at 12.7 and 13.7 ppb. The average concentration of melengestrol acetate in fat samples from the 3X and 5X dose groups were 37.6 ppb (range 30.9 to 46.3 ppb) and 49.4 ppb (range 36.6 to 57.0 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 lasalocid and tylosin residues. No residues of tylosin were detected in any of the samples. The limit of detection for the assay utilized was 0.1 ppm.
- No lasalocid was detected in the liver samples from the control heifers. Lasalocid was detected in the liver samples from each of the 7 heifers in the 1X group with a mean and standard deviation of 0.09 +/- 0.11 ppm. The highest individual value was 0.26 ppm. All concentrations of lasalocid were well below the tolerance limit of 0.7 ppm in liver.

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

C. Assay noninterference

Data included in previous Freedom of Information Summaries for these NADA's have demonstrated;

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

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

It has also been demonstrated that the presence of melengestrol acetate does not interfere with the tissue residue assay for lasalocid (NADA 96-298; J.Agri. Food Chem. 31:75-78:1983).

D. Regulatory methods

Practical regulatory methods for analysis of tissue residues of melengestrol acetate, lasalocid 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 deletion of the requirement for a 48 hour pre-slaughter drug withdrawal period when melengestrol acetate and lasalocid are fed in combination either with or without tylosin. No changes are made in either the approved dosages of any of these drugs, the approved indications of use or in the target class of livestock. The data submitted support the conclusion that residues of melengestrol acetate in fat are below the established tolerance for melengestrol acetate when heifers are slaughtered without a pre-slaughter withdrawal following the combined feeding of melengestrol acetate, lasalocid and tylosin. Accordingly, approval of this change in pre-slaughter withdrawal period from 48 hours to no withdrawal 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 either with lasalocid or with lasalocid and tylosin. 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. LABELING (ATTACHED)

1) Bag or bulk Medicated Heifer Dry Supplement (Type B Medicated Feed) containing MGA and lasalosid
2) Medicated Liquid Heifer Supplement (bulk only) containing MGA and lasalosid
3) Bag or bulk Medicated Heifer Dry Supplement (Type B Medicated Feed) containing MGA, lasalosid 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

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.