Approval Date: July 2, 1996

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-897

B. Sponsor

Roussel Uclaf
Division Agro-veterinaire
102, route de Noisy
93230 Romainville, France

C. Proprietary Name

REVALOR®-G

D. Established Name

trenbolone acetate and estradiol

E. Dosage Form

implantation

F. Dosage Regimen

One implant containing 40 mg trenbolone acetate and 8 mg estradiol. Each implant is made up of two pellets with each pellet containing 20 mg trenbolone acetate and 4 mg estradiol. Each implant is contained in one division of a multiple dose cartridge. There are ten doses in each cartridge. The cartridge is designed to be used with a special implant gun which places the implant under the skin on the posterior aspect of the ear.

G. Route of Administration

Subcutaneous implantation on the posterior aspect of the middle one-third of the ear by means of an implant gun

H. Indication

For increased rate of weight gain in pasture cattle (slaughter, stocker and feeder steers and heifers).

I. Effect of Supplement

Provides for the administration of REVALOR®-G in pasture heifers (slaughter, stocker and feeder heifers) for increased rate of weight gain.

II. EFFECTIVENESS

The supplemental new animal drug application for REVALOR-G contains data from adequate and well-controlled studies demonstrating the effectiveness of the new animal drug for the indications for use and dosage as given in Sections 2 and 3 above.

Pivotal Studies:

The pivotal studies are dose titration studies in which the parameters measured are the same parameters as are measured in field investigations. Four dose titration studies were conducted using a uniform protocol so that the results of the studies could be pooled and summarized. The studies were conducted in the major beef producing areas of the United States.

Name and Address of Investigators:

Dr. Daryl Meyer (Nebraska Study)
Lucerne Enterprises
Fremont, Nebraska

Dr. Mary Wray (Virginia Study)
Horton Feedlot and Research Center
Wellington, Colorado

Dr. Jeff Davidson (California Study)
Health Management Services
Tulare, California

Dr. E. G. Johnson (Idaho Study)
Johnson Research
Parma, Idaho

The purpose of the studies was to evaluate the dose response for trenbolone acetate (TBA) and estradiol (E2beta) on average daily gain of heifers maintained on pasture. The test animals were straight-bred and cross-bred animals of European and Exotic breeds. For each study, 300 heifers were blocked by weight (six heifers/block) and randomly assigned within block to one of six treatments (50 replicates/treatment). The treatments consisted of Control (no implant), 10 mg E2beta, 40 mg TBA, 2 mg E2beta/10 mg TBA, 4 mg E2beta/20 mg TBA, and 8 mg E2beta/40 mg TBA. The average weights of heifers for each study were between 475 lbs. and 593 lbs. when the studies were initiated. The duration of the studies ranged between 96 and 114 days. Each heifer was administered TBA and E2beta via subcutaneous implantation on the backside of the mid-ear. The heifers were administered the implant once at the initiation of each study. After the cattle were implanted they were maintained together in the same pasture for the duration of the study.

Average daily gain (ADG) data for the heifers are summarized in Table 1 for each of the four dose titration studies.

A randomized complete block design was used for all four studies and the data were pooled by analysis of variance to determine the significance of the effect of TBA/E2beta implants on ADG. There was a significant ($P<.01$) linear response in ADG to increasing levels of the combination product with the maximum response seen at the highest dose (8 mg E2beta /40 mg TBA). The 8 mg E2beta /40 mg TBA treatment also was shown to

be significantly (P < .05) better than 40 mg TBA alone and 10 mg E2beta alone. These data are sufficient to support the claims and dosage as provided in Sections 2 and 3.

TABLE 1. SUMMARY OF RESULTS FOR AVERAGE DAILY GAIN (LBS.)

E2beta/TBA (mg/mg)	Location-Idaho	Location - Virginia	Location - Nebraska	Location-California	Pooled LS Means
0 / 0	1.883	1.338	1.608	1.654	1.621
10 / 0	1.852	1.372	1.631	1.891	1.686
0 / 40	1.884	1.448	1.499	1.640	1.618
2 / 10	1.869	1.423	1.619	1.845	1.689
4 / 20	1.858	1.431	1.754	1.823	1.717
8 / 40	1.971	1.485	1.903	1.982	1.835

III. TARGET ANIMAL SAFETY

The supplemental new animal drug application for REVALOR-G references the target animal safety studies summarized in the FOI for NADA 140-992 (60 FR 4376 - January 23, 1995). The data from those studies demonstrate the safety of the new animal drug for the indications for use and dosage as given in Sections 2 and 3 above.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests

The toxicity studies summarized in the FOI from NADA 138-612 (52 FR 24994 - July 2, 1987) have met the Agency's requirement for human food safety for TBA. Allowable incremental increases of estradiol have been established by the Agency under 21 CFR 556.240.

B. Safe Concentration of Residues

Under NADA 138-612 (TBA), it was determined that the safe concentration for total residues of trenbolone was 50 ppb for muscle, 100 ppb for liver, 150 ppb for kidney, and 200 ppb for fat (21 CFR 556.739). The total average trenbolone residues in the livers of animals treated with 200 mg 3H-TBA were determined to be 43.8 ppb and 50.5 ppb at 15 and 30 days, respectively. The residues in muscle, kidney, and fat were much lower.

C. Residue Depletion Study

A tissue residue study was conducted to determine the residues of estradiol and the two metabolites of TBA (17alpha-hydroxytrenbolone (17alpha-TBA) and 17beta-hydroxytrenbolone (17beta-TBA)) in heifers treated with 180 mg TBA + 18 mg estradiol. The results of the estradiol assays from the treated and control animals were compared to the allowable incremental increases permitted under 21 CFR 556.240. When the residues of estradiol in the treated animals were compared to the naturally occurring levels in the untreated controls, they were found to be much lower than the allowable

incremental increases. For trenbolone acetate residues, the purpose of the study was to determine the residue levels in the treated animals and compare them to the residues incurred with the approved Finaplix-H implant (200 mg trenbolone acetate alone). Liver residues of 17beta-TBA resulting from the use of 180 mg TBA/18 mg estradiol were not statistically different from the residues of 17beta-TBA resulting from the use of 200 mg TBA alone at either 15 or 30 days postimplantation. Furthermore, the combined levels of 17alpha-TBA and 17beta-TBA were less than the combined amounts of these residues for the 200 mg TBA implant which is approved. This study is summarized in the FOI Summary from NADA 140-992 (60 FR 4376 - January 23, 1995).

Since the dose of TBA and estradiol are significantly lower for Revalor-G (pasture heifers) than the dose approved for Revalor-H (feedlot heifers), additional residue studies were not required for this approval.

D. Withdrawal Period

Residues of estradiol in heifers treated with Revalor-H were many times lower than the allowable incremental increases permitted under 21 CFR 556.240. Residues of 17beta-TBA in the tissues of heifers treated with Revalor-H were not statistically different from the residues of 17beta-TBA resulting from the use of 200 mg TBA alone. The combined trenbolone levels (17alpha-TBA + 17beta-TBA) were lower in heifers treated with Revalor-H than in heifers treated with 200 mg TBA alone. As such, a withdrawal period was not required for the approval of Revalor-H.

Since the dose of TBA and estradiol are significantly lower for Revalor-G (pasture heifers) than the dose approved for Revalor-H (feedlot heifers), a withdrawal time likewise is not required for this approval.

E. Regulatory Method

Since a withdrawal period is not required for the use of Revalor-G, neither a regulatory or confirmatory method was required for this approval.

V. AGENCY CONCLUSIONS

Adequate data were provided to demonstrate the safe and effective use of Revalor-G (ear implant containing 40 mg TBA and 8 mg estradiol) when used in pasture heifers (slaughter, stocker and feeder heifers) for increased rate of weight gain.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the use of an ear implant containing 40 mg TBA and 8 mg estradiol in pasture heifers. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the supplemental application contains reports of new clinical investigations (other than bioequivalence or residue studies) essential to the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the change for which the supplemental application was approved, i.e., use of an ear implant containing 40 mg TBA and 8 mg estradiol in pasture heifers.

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.