Approval Date: November 27, 1991

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-897

B. Sponsor

Roussel UCLAF
Division Agro-veterinaire
163 Avenue Gambetta
75020, Paris, France

C. Proprietary Name

REVALOR®-S

D. Established Name

trenbolone acetate and estradiol

E. Dosage Form

An ear implant for feedlot steers

F. Dosage Regimen

One implant contains 120 mg trenbolone acetate and 24 mg estradiol. Each implant is made up of six 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. Steers entering the feedlot will be implanted with this product.

G. Route of Administration

Subcutaneous implantation on the posterior aspect of the ear by means of an implant gun.

H. Indication

For increased rate of weight gain and improved feed efficiency in feedlot steers.

II. EFFECTIVENESS

Pivotal Studies:

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

A. Dose Titration Trials

In dose titration studies the parameters measured are the same parameters as are measured in field investigations. The 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. Rodney Preston
Texas Tech University
College of Agricultural Science
Dept. of Animal Science
Lubbock, TX 79409-4109

Dr. Darrel Meyer
Meyer Feedlot and Research Center
Route #2, Box 23-A
Gothenburg, NE 69138

Dr. Dallas Horton
Horton Feedlot and Research Center
5100 East County Road 70
Wellington, CO 80549

The purpose of the studies was to determine the dose response for trenbolone acetate (TBA) and estradiol (E2Beta) ear implants on rate of weight gain and feed efficiency of confined steers. The test animals were cross-bred animals of European breeds. There were 7 to 10 animals per pen depending on study location. Each treatment was replicated 8 times (8 pens/treatment) in all three studies. The steers weighed between 700 (318 kg) to 750 (341 kg) lbs. when the studies were initiated. Eight hundred sixty-four steers were treated in these three dose titration studies.

REVALOR®-S was given via ear implants. The implants were placed subcutaneously on the back side of the mid-ear. Each dose was made up of the appropriate number of pellets, with each pellet containing 20 mg trenbolone acetate and 4 mg estradiol. The control cattle were not implanted. The dosages given in each study were (TBA/E2Beta): 0/0, 140/0, 0/30, 20/4, 80/16, and 140/28. The steers were implanted once at the initiation of the study. The termination of the studies ranged between 144 and 160 days.

Average daily gain and feed efficiency data are summarized in Table 1 for each of the three dose titration studies.

TABLE 1. SUMMARY FROM THREE DOSE TITRATION STUDIES COMPARING THE PERFORMANCE OF FEEDLOT STEERS ON VARIOUS LEVELS OF TRENBOLONE ACETATE AND ESTRADIOL

Average Daily Gain (lbs)

TBA/E2Beta (mg/mg)	Location - Texas	Location - Colorado	Location - Nebraska	Pooled Average
0/0	2.10	3.18	3.22	2.83
140/0	2.07	3.18	3.34	2.86
0/30	2.37	3.24	3.49	3.03
20/4	2.34	3.27	3.49	3.03
80/16	2.56	3.54	3.67	3.26
140/28	2.67	3.66	3.69	3.34

Feed Efficiency (lbs Dry Matter/lb Gain)

TBA/E2Beta (mg/mg)	Location - Texas	Location - Colorado	Location - Nebraska	Pooled Average
0/0	6.44	6.24	5.89	6.19
140/0	6.52	6.09	5.73	6.11
0/30	6.04	6.28	5.69	6.00
20/4	6.21	6.15	5.61	5.99
80/16	5.79	5.97	5.39	5.72
140/28	5.57	5.79	5.44	5.60

A randomized complete block design was used for all studies and the data were pooled by analysis of variance to determine the significance of the effect of trenbolone acetate/estradiol implants on average daily gain and feed efficiency. There was a significant ($P < .05$) dose effect on both average daily gain and feed efficiency with the maximum response for both parameters plateauing at a dose of 120 mg trenbolone acetate and 24 mg estradiol. The 120 mg TBA/24 mg E2Beta was also shown to be significantly ($P < .05$) better than 140 mg TBA alone and 30 mg E2Beta alone. These data indicate that TBA and E2Beta are effective for the indications for use and dosage as given in Sections 2 and 3 above. The effects of treatment on carcass parameters (yield grade, quality grade, and marbling scores) and on the incidence of liver abscesses were evaluated at slaughter. At the 140 mg TBA/28 mg E2Beta dose, a 10% decrease in marbling scores was observed ($P < .05$). Because of this observed decrease in marbling scores, the following statement is required on the label: Studies have demonstrated that the administration of Revalor®-S can result in decreased marbling scores when compared to non-implanted steers. No effect of treatment was seen on yield grade or the incidence of liver abscesses.

B. Clinical Field Studies

Three clinical field studies were conducted to confirm the significant response observed in average daily gain and feed efficiency in the dose titration studies. These studies were conducted using a uniform protocol so that the results could be pooled and summarized. These studies were also conducted in the major beef producing areas of the United States.

The test animals were cross-bred animals of European breeds. There were seven (7) to eight (8) animals per pen depending upon study location. Each treatment was replicated five times (5 pens/treatment) at each location. The steers weighed

between 675 (307 kg) and 750 (341 kg) lbs at the initiation of these studies. A total of 230 animals was used for these field studies.

The steers were implanted (subcutaneously on the back side of the mid-ear) once at the initiation of the studies with 140 mg TBA/28 mg E2Beta or served as non-implanted controls.

A randomized complete block design was used for all studies and the data were pooled by analysis of variance to determine the significance of the effect of REVALOR®-S on average daily gain and feed efficiency. There was a significant ($P < .05$) improvement in both average daily gain and feed efficiency for the steers implanted with TBA/E2Beta when compared to the steers in the control groups (Table 2).

The investigators for these three (3) field studies were:

Dr. Rodney Preston
Texas Tech University
Dept. of Animal Science
Lubbock, TX 79409-4109

Dr. Daryl Meyer
Meyer Feedlot and Research Center
Route #2; Box 23-A
Gothenburg, NE 69138

Mr. Preston Grover
Colorado Beef, Division of Continental Grain
Lamar, CO 81052

TABLE 2. SUMMARY FROM THREE FIELD STUDIES COMPARING THE FEEDLOT PERFORMANCE OF STEERS GIVEN TBA/E2Beta WITH CONTROL STEERS

Location	Treatment	ADG (lbs)	F/G
Texas	Control	2.31	9.32
	TBA/E2Beta	2.89	8.10
Colorado	Control	2.96	7.64
	TBA/E2Beta	3.06	7.42
Nebraska	Control	2.01	8.63
	TBA/E2Beta	3.37	7.48

III. TARGET ANIMAL SAFETY

Drug Safety Study:

A target animal safety study was conducted by Dr. N. L. Roberts, Huntington Research Center, Huntington, Cambridgeshire, England. The purpose of the study was to assess the safety to beef cattle of trenbolone acetate and estradiol given subcutaneously as an ear implant. Thirty-two (8 per group) yearling cattle weighing approximately 407 lbs (185 kg) at the initiation of the study were given the following dosages of trenbolone acetate/estradiol: control (no implant), 140/28, 420/84 and 700/140 per animal. There

were four steers and four heifers in each of the four treatment groups. The cattle were implanted once at the beginning of the study and the study was terminated after 160 days. The parameters measured were clinical signs, body weights, clinical biochemistry, and histopathology.

The treatment of beef cattle with REVALOR®-S by subcutaneous implantation at 1.2, 3.5, and 5.8 times the use level did not result in any adverse effects on clinical health. Steers in all test groups and heifers in the high dose group showed treatment-related increases in overall weight gain compared with the control animals. No adverse treatment related changes of any toxicological significance were observed in hematological parameters. At termination of the study, no significant macroscopic abnormalities were observed on post-mortem examination, although prostate and seminal vesicle weights were significantly greater in treated steers and uterine and ovarian weights were greater in treated heifers, compared with controls. These changes were considered to be due to the hormonal action of the test materials. On histopathological examination of tissues from the control and high dose group, both prostate and seminal vesicles showed moderate glandular development with secretion in treated steers as compared with poor development in controls as a result of castration. In females, mammary acinar development was moderate in treated animals and minimal in controls. No other microscopic changes of significance were observed. These changes were considered to be due to the hormonal action of the test materials.

A drug tolerance study is not needed because there is no likelihood of accidental overdosing with the use of ear implants.

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 requirements for human food safety for trenbolone acetate. Acceptable safe incremental increases above naturally occurring levels of estradiol have been established by the agency in 21 CFR Section 556.240. The data in NADA 140-897 demonstrate that estradiol tissue levels are well below the established permitted increases when used in combination with trenbolone acetate.

B. Safe Concentration of Residues

Data in the NADA for trenbolone acetate alone (NADA 138-612; 52 FR 24994-July 2, 1987) show that the safe concentration for total residues was 50 ppb for muscle, 100 ppb for liver, 150 ppb for kidney and 200 ppb for fat. The total average trenbolone residues in the liver of cattle treated with 200 mg of 3H-trenbolone acetate were determined to be 43.8 ppb at 15 days after implantation and 50.5 ppb after 30 days. The residues in muscle, kidney, and fat were much lower. In the tissue residue study summarized in Section 6.C of this FOI, the residues of trenbolone acetate in cattle implanted with REVALOR®-S are lower than the residues found in cattle implanted with 200 mg trenbolone acetate only. Therefore, with the residues at 15 and 30 days post-implantation being of adequate safety margins and trenbolone acetate residues from cattle treated with REVALOR®-S being lower than the residues from cattle implanted with an approved use of trenbolone acetate only, a 0-withdrawal period was established. Additionally it is not expected that any animals will be intentionally slaughtered within 15 days after implantation. Therefore, identification of a marker residue was not required.

In the tissue residue study summarized in Section 6.C. of this FOI, the residues of estradiol are well below the safe incremental levels established in 21 CFR Section 556.240. Therefore an adequate safety margin for estradiol residues has been established and no withdrawal period is required.

C. Residue Depletion Study

A tissue residue study was conducted to determine the residues of estradiol and the two metabolites of trenbolone acetate (17alpha-hydroxytrenbolone and 17Beta-hydroxytrenbolone). This study was conducted by Dr. Don Henricks, at Clemson University, Clemson, S.C. Eight (8) steers were treated with 140 mg trenbolone acetate and 28 mg estradiol. An additional eight (8) steers were treated with 200 mg trenbolone acetate. There were also four (4) control steers in the study. In each of the treatment groups, four steers were sacrificed 15 days after treatment and the other four steers were sacrificed 30 days after the initial implantation. Muscle, fat, liver, and kidney samples were collected from each animal on each of the sacrifice dates. After collection, the samples were immediately frozen in dry ice and held frozen until they were assayed for 17alpha-hydroxytrenbolone, 17Beta-hydroxytrenbolone and estradiol residues. The following two tables summarize the results from this study. As residue levels were similar at the 15 and 30 day sampling, the results in the following two tables are averaged across both sampling dates for the treated animals. Estradiol residues were assayed in only the control steers and steers treated with 140 mg TBA and 28 mg estradiol.

In Table 3, the results from the estradiol tissue assays are summarized. The results of the estradiol assays from the treated and control animals are compared with the acceptable safe incremental increases above naturally occurring levels established in 21 CFR Section 556.240. The estradiol levels from the treated and control animals were many times lower than the acceptable safe incremental levels. Since the acceptable safe incremental increases of estradiol exceed the estradiol levels found in the treated steers by such a wide margin, it was concluded that no pre-slaughter withdrawal period and no withholding restrictions were necessary. Thus there is no need for a regulatory tissue assay method for estradiol.

TABLE 3. ESTRADIOL LEVELS OF TREATED AND CONTROL STEERS COMPARED TO ESTABLISHED SAFE INCREMENTAL LEVELS

	Estradiol (ppt)		
Tissue	**Acceptable Increments**	**Revalor-S (No Withdrawal)**	**Untreated Controls**
Muscle	120	<6.0	<6.0
Fat	480	16.1 ±2.6	6.1 ±1.7
Kidney	360	<25.0	<25.0
Liver	240	<25.0	<25.0

The residues of 17alpha-hydroxytrenbolone and 17Beta-hydroxytrenbolone are reported in Table 4. When the residues of the two trenbolone metabolites are compared between the two implant groups, the residues from the implant containing 140 mg TBA/28 mg E2Beta are consistently lower than the residues from the steers implanted with only trenbolone acetate (200 mg). Thus, implanting cattle with the combination product (REVALOR®-S) gave trenbolone residues that were lower

compared to the residues when trenbolone is implanted alone. Additional information on the residues of trenbolone acetate can be found in the Freedom of Information Summary for NADA 138-612 (52 FR 24994-July 2, 1987).

TABLE 4. 17alpha-HYDROXYTRENBOLONE (TB-alpha) AND 17Beta-HYDROXYTRENBOLONE (TB-Beta) RESIDUES IN STEER TISSUES

TB-alpha (ppt)

Treatment (Implant)	**Tissue - Muscle**	**Tissue - Fat**	**Tissue – Liver**	**Tissue – Kidney**
Control	<15*	<30	<125*	<250
140 mg TBA/28 mb E2Beta	<15	<30	285 ± 114.8	<250
200 mg TBA	<15	126.9 ± 102.3	2899.0 ± 009.7	--

TB-Beta (ppt)

Treatment (Implant)	**Tissue - Muscle**	**Tissue - Fat**	**Tissue – Liver**	**Tissue – Kidney**
Control	<30	<30	<125	<250
140 mg TBA/28 mb E2Beta	75.6 ± 14.6	176.6 ± 48.1	199.9 ± 50.1	<250
200 mg TBA	175.0 ± 62.3	753.8 ± 138.2	629.7 ± 181.7	362.4 ± 56.0

* Limit of detection

D. Withdrawal Period

As discussed above, no withdrawal period is required following the use of trenbolone acetate and estradiol.

E. Regulatory Method

As discussed above, no withdrawal time is required. Therefore it is not necessary to have a regulatory assay method or a confirmatory assay method for trenbolone acetate or estradiol tissue residues. The respective RIA procedures for trenbolone acetate and estradiol were checked for cross-reactivity with the anti-sera of the other and it was concluded that no interference existed.

V. AGENCY CONCLUSIONS

The Center for Veterinary Medicine has concluded that the data submitted in support of this New Animal Drug Application satisfy the requirements of Section 512 of the Act. The data demonstrate that REVALOR®-S (trenbolone acetate and estradiol) is safe and effective to increase the rate of weight gain and improve feed efficiency in feedlot steers, when used in accordance with its labeled conditions of use. REVALOR®-S was shown to provide improvement over each compound used alone, in compliance with 21 CFR 514.1(b)(8)(v).

The patent number and expiration date for the combination of TBA and estradiol, as provided by the firm is: Patent no. 3,939,265 expires 2/17/93. Under Section

512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this NADA qualifies for three years of marketing exclusivity because new clinical or field investigations (other than bioequivalence or residue studies) were essential to the approval of the application and conducted or sponsored by the applicant.

The Center has concluded that REVALOR®-S is safe for over-the-counter (OTC) use. Directions on the labeling and packaging are adequate and ear implantation is a common method of administration of this type product within the feedlot industry. Producers who use this product can be expected to safely and successfully accomplish implantation. Further, there is no special need to recognize a disease condition, the drug is not a "controlled substance," and after implantation there is no need for medical monitoring or evaluation of the treated animal. Accordingly, prescription restriction of this product is not warranted.

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.