FREEDOM OF INFORMATION SUMMARY
FOR
REVALOR®-IH (TRENBOLONE ACETATE AND ESTRADIOL)

1. GENERAL INFORMATION

NADA Number:	140-992
Sponsor:	Hoechst Roussel Vet P.O. Box 4010 Clinton, NJ 008809
Generic Names:	Trenbolone Acetate and Estradiol
Trade Name:	Revalor®-IH
Marketing Status:	Over the counter (OTC)
Effect of Supplement:	Provides for the administration of a dose of 80 mg trenbolone acetate and 8 mg estradiol in heifers fed in confinement for slaughter for increased rate of weight gain. (Note: The sponsor currently has an approved implant containing 140 mg trenbolone acetate and 14 mg estradiol (Revalor® - H) - see 21 CFR 522.2477.)

2. INDICATIONS FOR USE

For increased rate of weight gain in heifers fed in confinement for slaughter.

3. DOSAGE FORM(S), ROUTE(S) OF ADMINISTRATION AND RECOMMENDED DOSAGE

Dosage Form:	Implantation
Route of Administration:	Subcutaneous implantation on the posterior aspect of the ear.
Recommended Dosage:	One implant containing 80 mg trenbolone acetate and 8 mg estradiol. Each implant is made up of 4 pellets with each pellet containing 20 mg trenbolone acetate and 2 mg estradiol.

4. EFFECTIVENESS

This supplemental new animal drug application for Revalor®-IH references the efficacy studies summarized in the FOI for NADA 140-992 (60 FR 4376 – January 23, 1995). The data from those studies demonstrate the efficacy of the new animal drug for the indication for use and dosage as given in Sections 2 and 3 above. The summary of the efficacy (Dose Titration) studies from the 1995 FOI is also presented below.

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.

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The purpose of the studies was to determine the dose response for trenbolone acetate (TBA) and estradiol (E2β) ear implants on rate of weight gain and feed efficiency of confined heifers. 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 heifers weighed between 585 (265 kg) and 639 (290 kg) lbs. when the studies were initiated. A total of 864 heifers were treated in these three dose titration studies.

The drug (TBA+estradiol) 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 2 mg estradiol. The control cattle were not implanted. The dosages given in each study were (TBA/E2β): 0/0, 200/0, 0/20, 80/8, 140/14 and 200/20. The heifers were implanted once at the initiation of the study. The termination of the studies ranged between 139 and 147 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 CONFINED HEIFERS ON VARIOUS LEVELS OF TRENBOLONE ACETATE AND ESTRADIOL

	Location			
TBA/E2β (mg/mg)	Texas	Colorado	Idaho	Pooled Average
Average Daily Gain (lbs)				
0/0	2.18	2.09	3.28	2.51
200/0	2.27	2.22	3.57	2.70
0/20	2.40	2.21	3.62	2.73
80/8	2.47	2.36	3.55	2.78
140/14	2.49	2.49	3.64	2.87
200/20	2.60	2.42	3.57	2.84
Feed Efficiency (lbs Dry Matter/lb Gain				
0/0	7.20	6.89	7.01	7.03
200/0	7.02	6.41	6.57	6.66
0/20	6.89	6.43	6.73	6.69
80/8	6.78	6.27	6.77	6.60
140/14	6.69	5.98	6.57	6.42
200/20	6.47	6.03	6.63	6.38

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 TBA/E2β 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 140 mg trenbolone acetate and 14 mg estradiol. For feed efficiency the 140 mg TBA/14 mg E2β mg dose was also shown to be significantly ($P<.05$) better than 200 mg TBA alone and 20 mg E2β alone. For average daily gain both the 80 mg TBA/8 mg E2β and 140 mg TBA/14 mg E2β doses were significantly ($P<.05$) better than 200 mg TBA alone and 20 mg E2β alone. A highly significant ($P<.001$) linear improvement in average daily gain and feed efficiency was observed. These data are sufficient to support the claims and dosage as provided in Sections 2 and 3.

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/14 mg E2β dose, a decrease in marbling scores was observed. No effect of treatment was seen in yield grade or the incidence of liver abscesses. Because of the observed decrease in marbling scores, the following statement is required on the label: Studies have demonstrated that the administration of Revalor®-IH can result in decreased marbling scores when compared to non-implanted heifers.

5. TARGET ANIMAL SAFETY

This supplemental new animal drug application for Revalor®-IH 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.

6. HUMAN SAFETY

A. Toxicity Tests and Safe Concentration

The toxicity studies summarized in the FOI from NADA 138-612 (52 FR 24994 - July 2, 1987) establish the safe concentration for TBA. An acceptable daily intake (ADI) of 0.0004 mg/kg body weight/day has been established for trenbolone (64 FR 18573). Estradiol is regulated under 21 CFR 556.240 on the basis of allowable incremental increases. Residues for estradiol and related esters may not exceed the following increments above the concentrations of estradiol naturally present in the untreated animals; in the uncooked edible tissues of heifers, steers, and calves, 120 parts per trillion (ppt) for muscle, 480 ppt in fat, 360 ppt for kidney, and 240 ppt for liver.

B. Residue Depletion Study

The residue depletion study is summarized in the FOI Summary for NADA 140-897 (56 FR 67175 - December 30, 1991).

C. Withdrawal Period

As summarized in the FOI Summary for NADA 140-897 (56 FR 67175 - December 30, 1991).

D. 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 TBA or estradiol tissue residues.

7. AGENCY CONCLUSIONS

Adequate data is established to demonstrate the safe and effective use of Revalor®-IH (ear implant containing 80 mg trenbolone acetate and 8 mg estradiol) when used in heifers fed in confinement for slaughter 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 Revalor®-IH in heifers fed in confinement for slaughter. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

8. LABELING

Facsimile labeling (for Revalor®-IH) is attached as follows:

1. Cartridge Label
2. Package Insert
3. Box Label – 100 doses
4. Box Label – 1000 doses
5. Box Label – 4000 doses
6. Outer Shipping Label