Approval Date: September 27, 2002

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-346

Trenbolone Acetate and Estradiol (COMPONENT® TE-H)

For increased rate of weight gain and improved feed efficiency for heifers fed in confinement for slaughter.

Sponsored by:

Ivy Laboratories
Division of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214

FREEDOM OF INFORMATION SUMMARY

Component® TE-H Ear Implant for Heifers Fed in Confinement for Slaughter

1. GENERAL INFORMATION

a. File Number: ANADA 200-346

b. Sponsor:
Ivy Laboratories
Division of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214
Drug Labeler Code: 021641

c. Established Names: Trenbolone acetate and estradiol

d. Propriety Names: Component® TE-H

e. Dosage Form: Implantation (ear implant) as per 21 CFR 522.2477.

f. How Supplied: As an implant made up of 7 pellets with each pellet containing 20 mg trenbolone acetate and 2 mg estradiol

g. How Dispensed: OTC

h. Amount of Active Ingredients: Trenbolone acetate: 140 mg trenbolone acetate activity.
Estradiol: 14 mg estradiol activity.

i. Route of Administration: Subcutaneous ear implant

j. Species/Class: Heifers fed in confinement for slaughter

k. Recommended Dosage: One implant containing 140 mg trenbolone acetate and 14 mg estradiol per animal.

l. Pharmacological Category: Steroid hormone

m. Indications: For increased rate of weight gain and improved feed efficiency for heifers fed in confinement for slaughter.

n. Pioneer Product: Revalor®-H
Trenbolone acetate and estradiol
NADA 140-992
Intervet.

2. EFFECTIVENESS

The abbreviated new animal drug application for Component® TE-H contains adequate data from a well-controlled investigation demonstrating bioequivalence of Component® TE-H to the parent drug, Revalor®-H. The bioequivalence study was conducted in a major beef producing area of the United States.

Materials and Methods:

Name and Address of Investigator:

Tony Janes, B.S.
CAVL, Inc.
9602 South Washington
Amarillo, TX 79118

The purpose of the study was to demonstrate bioequivalence of Component® TE-H to Revalor®-H through comparison of blood serum trenbolone-17β and estradiol-17β parameters in steers implanted with Component® TE-H and Revalor®-H.

One hundred ten steers were used as test animals in a 91 day study. Steers were used to eliminate the effects of endogenous estradiol from the ovary. Animals were housed in a single pen. Steers weighed between 508 and 581 lbs when the study was initiated. Component® TE-H and Revalor®-H were administered subcutaneously in the middle third of the ear with the respective implanting device. Cattle were weighed on Day 0 to serve as an initial weight and subsequently on Days 49 and 91 to monitor weight gain of the animals.

Blood samples were collected from Day -2 through Day 91 of treatment at regular predetermined intervals to monitor serum levels of trenbolone-17β and estradiol-17β by radioimmunoassay. Samples were collected on days -2, -1, 0 3, 5, 7, 9, and every 7 days from days 14 to 91.

Trenbolone-17β and estradiol-17β concentrations (pg/ml) for sample time periods were evaluated in two replicates. The natural log of the area-under-the-curve (log AUC)and the natural log of the maximum observed drug concentration (log CMAX) are identified as pivotal variables for extent of product bioavailability and rate of absorption, respectively, in "Guidance for Industry #35: Bioequivalence" (Docket No. 94D-0401, 2000). However, because implants have an extended duration of drug release with no single, clearly defined peak for determination of CMAX, alternative procedures were chosen. The log AUC for days 0 to 91 (extent of product bioavailability)and the natural log of partial areas-under-the-curve

(rate of absorption) were used as pivotal variables for bioequivalence determination. The partial area-under the curve variables were: natural log of the area-under-the-curve from day 0 to day 14 (log AUC1), natural log of area-under-the-curve from day 14 to day 56 (log AUC2), and natural log of area-under-the-curve from day 56 to day 91 (log AUC3). The partial areas (log AUC1, log AUC2 and log AUC3) were calculated from the mean of the sample time replicates.

Log AUC, log AUC1, log AUC2 and log AUC3 were analyzed using a completely random design. Endpoints for establishing bioequivalence for log AUC1, log AUC2 and log AUC3 were calculated to adjust for both the correlation between the treatment differences for the three areas and the use of three variables (areas) in the establishment of bioequivalence. The bioequivalence bounds for log AUC were -20% to +25% of the pioneer product at the 90% confidence level. Bioequivalence bounds of the partial areas were -25% to +33% of the pioneer product at the 90% confidence level.

Results:

The analysis of pivotal variables related to concentrations of Trenbolone-17β and Estradiol-17β, log AUC and three partial areas (log AUC1, log AUC2 and log AUC3), show that Revalor®-H and Component® TE-H are bioequivalent (see Tables 1 and 2). With respect to both Trenbolone-17β (Table 1) and Estradiol-17β (Table 2), the lower and upper limits for log AUC were within the -20% to +25% criterion, while the lower and upper limits for the partial areas (log AUC1, log AUC2 and log AUC3) were within the -25% to +33% criterion.

Conclusions:

Based on the results of this study, we conclude that Revalor®-H and Component® TE-H are bioequivalent.

Table 1. Test of Bioequivalence of Trenbolone-17β Based on log AUC and log AUC1, AUC2 and AUC3

Analysis Variable	LS Mean Component TE-H	LS Mean Revalor-H	Difference	Lower[e]	Upper[e]
LAUC[a]	9.6159	9.602	0.0139	-9.69%	12.89%
LAUC1[b]	8.0104	8.1544	-0.1440	-24.29%	-0.98%
LAUC2[c]	9.0254	8.9350	0.0904	-4.38%	25.33%
LAUC3[d]	8.0601	8.102	-0.0419	-18.17%	12.4%

[a]LAUC = natural log of the area-under-the-curve (days 0-91)
[b]LAUC1 = natural log of the area-under-the-curve (days 0-14)
[c]LAUC = natural log of the area-under-the-curve (days 14-56)
[d]LAUC = natural log of the area-under-the-curve (days 56-91)

[e]Lower and upper required bioequivalence endpoints for Component T-EH were from -20% to +25% of Revalor-H for LAUC and from-25% to +33% for the partial areas (LAUC1, LAUC2 and LAUC3).

Table 2. Test of Bioequivalence of Estradiol-17β Based on log AUC and log AUC1, AUC2 and AUC3

Analysis Variable	LS Mean Component TE-H	LS Mean Revalor-H	Difference	Lower[e]	Upper[e]
LAUC[a]	8.2599	8.2289	0.0310	6.69%	14.03%
LAUC1[b]	6.3015	6.2589	0.0426	-9.99%	20.99%
LAUC2[c]	7.6194	7.4659	0.1535	3.44%	31.40%
LAUC3[d]	7.0561	7.1941	-0.1380	-24.86%	1.00%

[a]LAUC = natural log of the area-under-the-curve (days 0-91)
[b]LAUC1 = natural log of the area-under-the-curve (days 0-14)
[c]LAUC = natural log of the area-under-the-curve (days 14-56)
[d]LAUC = natural log of the area-under-the-curve (days 56-91)

[e]Lower and upper required bioequivalence endpoints for Component T-EH were from -20% to +25% of Revalor-H for LAUC and from-25% to +33% for the partial areas (LAUC1, LAUC2 and LAUC3).

3. TARGET ANIMAL SAFETY AND EFFECTIVENESS

Under the provisions of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Action (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

4. HUMAN SAFETY

- Allowable Incremental Increases and Tolerances for Residues:

  The allowable incremental increases established for the pioneer product apply to the generic product. Estradiol is regulated under 21 CFR 556.240. No residues of estradiol, resulting from the use of estradiol or any of the related esters, are permitted in the uncooked edible tissues of heifers in excess of the following increments above the concentrations of estradiol naturally present in untreated animals: 120 ppt for muscle, 240 ppt for liver, 360 ppt for kidney, and 480 ppt for fat.

  The tolerances established for the pioneer product apply to the generic product. Trenbolone acetate is regulated under 21 CFR 556.739. The Acceptable Daily Intake (ADI) for total residues of trenbolone is 0.4 micrograms per kilogram body weight per day. A tolerance for trenbolone residues in uncooked edible tissues of cattle is not needed.

- Withdrawal Time:

  When a generic product demonstrates bioequivalence to the pioneer product in a blood level study where the duration of the study exceeds the withdrawal time assigned to the pioneer product, the generic product is assigned the withdrawal time established for the pioneer product. The zero withdrawal is established for implants containing trenbolone acetate and estradiol.

- Regulatory Method for Residues:

  A regulatory method is not required.

5. AGENCY CONCLUSIONS

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that the trenbolone acetate and estradiol (Component® TE-H), when used under its proposed conditions of use, is safe and effective for its labeled indications.

6. ATTACHMENTS

Facsimile Generic Labeling and Currently Approved Pioneer Labeling are attached as indicated below:

Box Label (Generic)
Foil Pouch Label (Generic)
Package Insert (Generic)
Box Label (Pioneer)
Cartridge Label (Pioneer)
Package Insert (Pioneer)