FREEDOM OF INFORMATION SUMMARY
FOR
SYNOVEX® PLUS (TRENBOLONE ACETATE & ESTRADIOL BENZOATE

1. GENERAL INFORMATION

NADA Number: 141-043

Sponsor: Syntex Animal Health
Division of Syntex Agribusiness, Inc.
3401 Hillview Avenue
Palo Alto, CA 94304

Generic Name: Trenbolone Acetate and Estradiol Benzoate

Trade Name: Synovex® Plus

Marketing Status: Over-The-Counter (OTC)

2. INDICATIONS FOR USE

For improved feed efficiency in steers fed in confinement for slaughter.

3. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

The dosage form is implantation. The route of administration is subcutaneous implantation on the posterior aspect of the middle one-third of the ear by means of an implant gun. The recommended dosage is one implant containing 200 mg trenbolone acetate (TBA) and 28 mg estradiol benzoate (EB). The implant consists of eight pellets with each pellet containing 25 mg TBA and 3.5 mg EB. Each implant is contained in one division of a ten dose cartridge. The cartridge is designed to be used with a Syntex implanting device.

4. EFFECTIVENESS

The new animal drug application contains data from adequate and well-controlled studies demonstrating the effectiveness of Synovex® Plus 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. Three dose titration studies were conducted using a uniform protocol so that the results of the studies could be pooled and summarized. The three studies were conducted in major beef producing areas of the United States.

Name and Address of Investigators:

James J. Sheldon, D.V.M., Ph.D.
Sheldon Agri-business
Casa Grande, Arizona.
Study Location: El Centro, CA

Rodney L. Preston, Ph.D.
Texas Tech University
Department of Animal Science
Lubbock, Texas
Study Location: New Deal, TX

Alvin Edwards, D.V.M., Ph.D.
Kansas State University
College of Veterinary Medicine
Manhattan, KS
Study Location: Lamar, CO

The purpose of the studies was to evaluate the dose response for TBA and EB on feed efficiency of steers fed in confinement for slaughter. The test animals were cross-bred animals of Brahman, English, and Exotic breeds. For each study, 360 steers were randomized on the basis of weight into 5 blocks of 9 pens with 8 animals per pen, and administered one of the following treatments: 0/0, 0/300, 60/0, 20/70, 40/140, 60/210, 14/100, 28/200, and 42/300 (mg EB/mg TBA). The steers weighed approximately 600 pounds when the studies were initiated. The duration of the studies ranged between 132 to 183 days.

Each steer was administered EB/TBA via subcutaneous implantation on the backside of the mid-ear. The control steers were not implanted. The steers were implanted once at the initiation of each study.

Feed/gain (F/G) data for the steers are summarized in Table 1 for each of the three dose titration studies.

A combined statistical analysis (analysis of variance) of the data from the three studies was conducted for F/G. A significant difference ($p < .05$) was seen between the treatment groups. A simple linear model was seen to be the best fitting model with the 28 mg EB/200 mg TBA identified as the lowest dose significantly superior ($p < .05$) to both single components. These data are sufficient to support the claim and dosage as provided in Sections 2 and 3.

The effects of treatment on yield grade, quality grade, marbling score, and liver abscess incidence were evaluated at slaughter. The 28/200 dose decreased marbling score 11% (2-side $p < .05$). No effect of treatment was seen in yield grade or the incidences 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 Synovex Plus can result in decreased marbling scores when compared to non-implanted steers.

TABLE 1. SUMMARY FROM THREE DOSE TITRATION STUDIES COMPARING THE EFFECT OF VARIOUS LEVELS OF TRENBOLONE ACETATE AND ESTRADIOL BENZOATE ON FEED EFFICIENCY IN FEEDLOT STEERS

	Location			
EB/TBA (mg)	Texas	Colorado	California	Pooled Average
0/0	7.00	5.43	5.14	5.86
0/300	6.37	5.32	5.38	5.69
60/0	6.37	5.69	4.86	5.64
14/100	6.15	5.32	5.02	5.50
28/200	6.20	5.32	4.78	5.43
42/300	6.08	5.12	4.77	5.32

5. TARGET ANIMAL SAFETY

The new animal drug application contains data from an adequate and well-controlled investigation demonstrating the safety of Synovex® Plus for the indications for use and dosage as given in Sections 2 and 3 above.

Pivotal Study:

A target animal safety study was conducted by Dr. James J. Sheldon, CAVL, Inc., P.O. Box 1296, Casa Grande, AZ. The purpose of the study was to assess the safety to feedlot steers of TBA and EB given subcutaneously as an ear implant. Six groups of 9 beef-type steers (English beef breeds and exotic breeds/Brahma, 231.8-302.3 kg) each were implanted once with 1, 3, or 5 implants containing either of two ratios of estradiol benzoate and trenbolone acetate. Ratio I (TBA/EB I) contained 40 mg of estradiol benzoate and 140 mg of trenbolone acetate. Ratio II (TBA/EB II) contained 28 mg of estradiol benzoate and 200 mg of trenbolone acetate. The implants were administered subcutaneously in the middle third of the back of the ear. The doses represented 1, 3, and 5 times the proposed clinical use level for each ratio. A seventh group of nine steers served as sham controls. The steers were observed daily and feed consumption and body weights were measured at approximately 4- to 5-week intervals designated as study periods. Hematology and clinical chemistry parameters were measured before dosing, at the ends of the first and fourth study periods, and at study termination. The study terminated approximately 180 days after implantation, at which time six of the nine steers per group were subjected to gross pathologic examination.

When compared with sham controls, the following clinical findings, considered to be pharmacological effects, were attributed to the treatment regimen: TBA/EB I – increased incidence of altered sheaths and increased incidence of masculinization; TBA/EB II – increased incidence of altered sheaths, increased incidence of raised tailhead, and increased incidence of masculinization. In all instances, the pharmacological effects were not present in steers at study termination. Neither ratio of TBA/EB at 1, 3, or 5 times the proposed use level caused adverse effects on any production factor. There were no treatment-related adverse effects on clinical pathology parameters or in gross pathologic findings in the steers implanted with either ratio of TBA/EB.

6. HUMAN FOOD SAFETY

A. **Toxicity Studies**:

1. **Twelve Month Oral Toxicity Study in Rats with Trenbolone Acetate - Syntex Research, Palo Alto, CA.**

Twenty-five male and 25 female CD® rats in each of 4 groups were provided diets containing TBA at 0.5, 1, 4, or 16 ppm, respectively, for 12 consecutive months. Twenty-five males and 25 females in a fifth group were provided a control diet and served as an experimental control. Clinical observations and body weights were recorded weekly and terminally. Food intake was recorded weekly. Ophthalmic examinations were performed before the first dose, after approximately 3, 6, and 9 months of dosing, and near the end of treatment. Clinical pathology evaluations were conducted after approximately 3, 6, and 9 months of dosing and near the end of treatment. Rats found dead, killed for cause, or surviving to the end of the study received necropsy examinations.

There were no treatment-related clinical signs attributed to treatment with TBA. There were five unscheduled deaths during the study in either the control or 0.5-ppm group; none were attributed to TBA administration. There were no treatment-related differences in body weight or food intake of rats given TBA. No treatment-related eye abnormalities were present. There were no treatment-related hematological or clinical chemistry changes present in any TBA-treated male groups or in females given 0.5, 1, or 4 ppm of TBA. The erythrocyte counts and hematocrit measurements of females given 16 ppm were slightly, but statistically significantly higher than those of the control females at all intervals evaluated. Serum levels of bilirubin, total protein, and albumin were slightly, but statistically significantly lower than control values for females given 16 ppm of TBA. The individual hematological and serum chemistry values were within the 95 percentile of in-house reference values.

Males had higher spleen weights and ratios and females had lower liver weights and ratios in the 16-ppm TBA group, when compared with control animals.

Females given TBA had treatment-related histological changes in the uterus and mammary gland when compared with the control females. Uterine lumen dilation was more frequent and/or severe in the 4 and 16 ppm TBA-treated female groups. Mammary gland atrophy was more severe and frequent in the 16 ppm TBA group, and mammary secretion was more commonly absent in this group. No other histopathological changes were attributed to TBA administration.

No treatment-related effects were present in male rats given 0.5, 1, 4, or 16 ppm of TBA and in female rats given 0.5 or 1 ppm of TBA in the diet for 12 months. Female rats exhibited uterine lumen dilation at 4 and 16 ppm of TBA and mammary gland atrophy at 16 ppm of TBA.

A NOEL of 1 ppm for TBA was established based on increased uterine dilation.

2. **Twelve Month Toxicity Study in Rhesus Monkeys with Trenbolone Acetate - Syntex Research, Palo Alto, CA.**

Five male and 5 female rhesus monkeys in each of 3 groups were given single daily oral doses of 10, 40, or 160 μg/kg/day of TBA for approximately 52 weeks. Five males and 5 females in a fourth group were given the vehicle for TBA and served as an experimental control. Clinical observations and body weights were recorded weekly and terminally for each monkey. Ophthalmologic examinations were performed on each monkey before the first dose, approximately every 3 months thereafter, and near the end of dosing. Blood samples for evaluation of hematological, clinical chemistry, and coagulation parameters were collected before the start of dosing, approximately every 3 months thereafter, and terminally. At the end of dosing, all surviving monkeys were evaluated for gross and microscopic pathologic changes.

No treatment-related clinical changes occurred. No treatment-related deaths occurred. One male given 40 μg/kg/day died from an accidental cause during study week 36. No TBA-related differences in body weight occurred. No TBA-induced ocular lesions were present. No TBA-related changes occurred in hematology, clinical chemistry, or coagulation parameters. Lower testicular weights were present in high-dose monkeys. There were no treatment-related pathologic changes in any of the organs/tissues including the reproductive organs of male and female monkeys. No clinical, clinical pathology, or anatomic pathology effects were present following daily oral administration of TBA for 12 months at doses of 10, 40, or 160 μg/kg/day to rhesus monkeys. The following were considered treatment related effects: (1) interruption of menstrual cycle in mid and high dose females, (2) small prostate and seminal vesicles in high dose males, small testes in mid and high dose groups, (3) low mean accessory sex organ weight in high dose males, (4) low testicular weights in mid and high dose groups, (5) decrease in spermatozoa numbers in mid and high dose group males, (6) increased severity and incidence of prostate gland hypoplasia in mid and high dose group males, (7) increased severity and incidence of seminal vesicle hypoplasia in high dose males, and (8) increased severity and incidence of hypospermia in mid and high dose males. The no observed effect level was 10 μg/kg/day.

3. **Oral Teratology Study in Rats with Trenbolone Acetate - Syntex Research, Palo Alto, CA.**

Twenty-seven female CD® rats with evidence of mating were administered doses 5, 10, and 20 mg/kg/day TBA from days 7 through 16 of gestation. A similar group of 27 female rats was administered vehicle formulation. The day of mating was designated day 1 of gestation. Clinical observations, body weight, and food intake were recorded at least weekly starting with day 1 of gestation. On day 21 of gestation, the animals were necropsied.

There were no treatment-related clinical changes, except salivation in the groups given 10 or 20 mg/kg/day. Four dams that died or were euthanized due to debilitated condition had evidence of malintubation or pneumonopathy. Average body weight gain and food intake of the groups given 10 or 20 mg/kg/day of TBA were significantly lower than controls during the dosing period. The body weight gain and food intake were comparable at termination of the study. There were no treatment-related changes in

uterine weights; number of implants, resorptions, or live fetuses; the proportion of male fetuses per litter; and fetal weight. No compound-related external, visceral, or skeletal anomalies were present in the fetuses of any group given TBA. Oral doses of 0 (vehicle) or 5, 10, or 20 mg/kg/day of TBA on gestation days 7 through 16 were not teratogenic in rats. At 10 or 20 mg/kg/day, there was a decreased maternal body weight gain and food intake during the treatment period. Fetal effects were apparent in the lower fetalweights for male fetuses in the 10 and 20 mg/kg/day groups. A NOEL of 5 mg/kg/day was found for both maternal and fetal effects in this study.

4. **Multigeneration Reproduction Study of Orally Administered Trenbolone Acetate in the Rat - Syntex Research, Palo Alto, CA.**

   For this two-generation reproduction study, 30 male and 30 female CD® rats in each of 3 groups (designated P1) were fed a diet containing TBA at 0.1, 0.5, or 5.0 ppm, respectively, for at least 10 weeks before mating (males) or for at least 2 weeks before mating (females) until after the F1 pups were weaned. Thirty males and 30 females in a fourth group were fed a control diet by the same regimen and served as the P1 control group. Weanling F1 rats (designated P2 generation) were randomly selected and were fed the same TBA diets as their parents until after weaning of the F2 generation. Clinical observations and body weights were recorded at least weekly, on the day a female had evidence of mating, and terminally. Food intake was recorded weekly for P1 and P2 females. Food intake for P1 and P2 males was recorded weekly until cohabitation began.

   In this study, there were no adverse effects on the fertility and reproduction of rats in either generation administered TBA in the diet at concentrations of 0.1, 0.5, or 5.0 ppm. The pregnant P1 females in the 5.0-ppm group had statistically significant lower body weights than the control group values during pregnancy and lactation.

   The no observed effect level is 5 ppm in the diet.

5. **The Effects of Orally Administered Trenbolone Acetate on Menstrual Cycles of Rhesus Monkeys - Syntex Research, Palo Alto, CA.**

   A total of 24 normal, cycling females were monitored through six consecutive menstrual cycles or the equivalent period. The first three cycles served as untreated control periods to establish normal menstrual cycle values for each monkey. At the start of cycle four, monkeys were randomly assigned to 1 of 4 groups. Three groups, each composed of 6 females, received 10, 50, or 250 μg/kg/day of TBA once daily for at least three consecutive menstrual cycles or a minimum of 75 days if no mense was observed. A control group, composed of 6 females, was administered the vehicle for TBA following the same regimen. No monkeys were necropsied at the end of the last cycle. Animals were observed twice daily for clinical signs of toxicity and/or general condition. Body weights were recorded on the first day of each cycle. Evidence of menstrual bleeding was recorded daily. Blood samples for evaluation of hematological and clinical chemistry parameters were collected during the first week of the first control cycle. Blood samples for evaluation of selected hematological parameters were collected on day 1 of the succeeding cycles. Blood samples for the determination of estradiol, progesterone, LH, and FSH were collected daily in the mornings of the third control and

third treatment cycles (CC3 and TC3), respectively, before dosing (TC3), starting on mense day 2. Blood samples for the determination of progesterone alone were collected every 3 days in the morning during TC1 and TC2, starting on day 3. Serum gonadotropin (FSH and LH) concentrations were analyzed by heterologous RIA methods at PRL. Serum levels of steroids (progesterone and estradiol) were determined by an HPLC-RIA method at Syntex Research.

Female rhesus monkeys were administered TBA orally for three consecutive menstrual cycles at doses of 10, 50, or 250 μg /kg/day. There appeared to be drug-related effects in the mid-dose (50 μg/kg) group. In this group two monkeys showed prolonged menstrual cycles and progesterone levels were indicative of a lack of ovulation during these cycles. The peak areas of estradiol and progesterone were substantially smaller than controls. The data was most consistent with a NOEL of 10 μg /kg/day.

6. **Mutagenicity Assays**

Ames Salmonella/Reverse Mutation Assay with TBA and Metabolites, TBA-17αOH and TBA-17βOH

SOURCE	LABORATORY	ASSAY CONDITION	DOSE (Range)	TESTER STRAINS	RESULTS
Syntex	Microbiological Associates, Inc. 9900 Blackwell Rd. Rockville, MD 20850	In vitro, with and without metabolic activation	10 μg to 4000 μg of TBA per plate	Salmonella typhimurium	
				TA-1535	Negative
				TA-1537	Negative
				TA-1538	Negative
				TA-98	Negative
				TA-100	Negative
Syntex	Microbiological Associates, Inc.	In vitro, with and without metabolic activation	100 μg to 5000 μg of 17αOH per plate	Salmonella typhimurium	
				TA-1535	Negative
				TA-1537	Negative
				TA-1538	Negative
				TA-98	Negative
				TA-100	Negative
Syntex	Microbiological Associates, Inc.	In vitro, with and without metabolic activation	100 μg to 5000 μg of 17βOH per plate	Salmonella typhimurium	
				TA-1535	Negative
				TA-1537	Negative
				TA-1538	Negative
				TA-98	Negative
				TA-100	Negative

The results were negative for all three test articles in both the presence and absence of exogenous metabolic activation. TBA, 17α-OH-trenbolone, and 17β-OH-trenbolone were considered negative in Ames Salmonella/reverse mutation assay.

Unscheduled DNA Synthesis in Rat Primary Hepatocyte with TBA and Metabolites, 17αOH and 17βOH

SOURCE	LABORATORY	ASSAY CONDITION	DOSE (Range)	TESTER SYSTEM	RESULTS
Syntex	Microbiological Associates, Inc. 9900 Blackwell Rd. Rockville, MD 20850	Uptake of 3H-thymidine into nuclei for 18-20 hours	0.75 to 50.0 μg of TBA per ml	DNA synthesis in rat primary hepatocyte cultures	Negative
Syntex	Microbiological Associates, Inc.	Uptake of 3H-thymidine into nuclei for 18-20 hours	0.25 to 25.0 μg of TB-17αOH per ml	DNA synthesis in rat primary hepatocyte cultures	Negative
Syntex	Microbiological Associates, Inc.	Uptake of 3H-thymidine into nuclei for 18-20 hours	0.20 to 20.0 μg of TB-17βOH per ml	DNA synthesis in rat primary hepatocyte cultures	Negative

TBA, TB-17αOH, and TB-17βOH were evaluated for their ability to induce unscheduled DNA synthesis in primary cultures of hepatocytes from male Fischer rats. The test articles were incubated using three replicate culture plates per dose level in the presence of tritiated thymidine. Exposed cells were evaluated using standard autoradiographic methods. The three test articles did not cause a significant increase in the mean number of net nuclear grain counts at any dose level. TBA, TB-17αOH, and TB-17βOH were considered negative in unscheduled DNA synthesis assay with rat primary hepatocytes.

CHO/HGPRT Mutation Assay with TBA and Metabolites TB-17αOH and TB-17βOH

SOURCE	LABORATORY	ASSAY CONDITION	DOSE (Range)	TESTER SYSTEM	RESULTS
Syntex	Microbiological Associates, Inc. 9900 Blackwell Rd. Rockville, MD 20850	In vitro, with and without rat liver S-9 metabolic activation	50 to 110 μg of TBA per ml	HGPRT gene mutation in CHO cell cultures	Negative
Syntex	Microbiological Associates, Inc.	In vitro, with and without rat liver S-9 metabolic activation	100 to 270 μg of TB-17αOH per ml	HGPRT gene mutation in CHO cell cultures	Negative
Syntex	Microbiological Associates, Inc.	In vitro, with and without rat liver S-9 metabolic activation	40 to 100 μg of TB-17βOH per ml	HGPRT gene mutation in CHO cell cultures	Negative
Syntex	Microbiological Associates, Inc.	In vitro, with rat liver S-9 metabolic activation	131 to 234 μg of TB-17αOH per ml	HGPRT gene mutation in CHO cell cultures	Negative

TBA, TB-17αOH, and TB-17βOH were evaluated for their ability to induce forward mutations at the HGPRT locus in CHO cell cultures. No significant increase in mutation frequency was observed in any of the test article-treated cultures, in both the presence and absence of exogenous metabolic activation. TBA, TB-17αOH, and TB-17βOH were considered negative in the CHO/HGPRT assay.

B. Safe Concentrations of Total Residue

The published safe concentrations of trenbolone in edible tissues are 50 ppb for muscle, 100 ppb for liver, 150 ppb for kidney, and 200 ppb for fat (21 CFR 556.739). The allowable increments for estradiol are 120 ppt for muscle and 480 ppt for fat (21 CFR 556.240).

C. Total Residue Depletion and Metabolism Study

1. Type of Study

A radiolabel study to determine the concentrations of [^{14}C] and 17β-estradiol in edible tissues of cattle following implantation with ^{14}C-trenbolone acetate and estradiol benzoate.

2. Investigator identifications

   a. In-Life Study Director:

      John W. Byrd M.S.
      Southwest Bio-Labs, Inc.
      401 N. 17th Street, #11
      Las Cruces, NM 88005
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   b. Analytical Study Director:

      Ian Massey, Ph.D.
      Syntex Development Research
      3401 Hillview Avenue
      Palo Alto, CA 94304
      Tel: (415) 855-6156

   c. Statistician:

      Ann Olmsted, M.S.
      Center for Biometrics and Data Management
      Syntex Development Research
      3401 Hillview Avenue
      Palo Alto, CA 94304
      Tel: (415) 852-1415

3. General Design of the Study:

   This study was conducted to examine the metabolism, excretion, and tissue residues of TBA following administration of an implant containing TBA in combination with EB. Additionally, fat and muscle tissue were evaluated for 17β-estradiol concentrations. Twenty-four cross-bred beef cattle (twelve steers and twelve heifers) weighing between 467 and 720 lbs were used in this study. The cattle were randomly divided into three equal groups. Each animal in Groups 1 and 2 received a single implant that was administered subcutaneously in the ear. Each implant contained 300 mg of ^{14}C-TBA and 42 mg of EB. The dose administered was 1.5 times the proposed dose (200 mg TBA and 28 mg EB). Animals in Group 3 served as untreated controls. Blood samples were collected from all animals on Study Days 0 (prior to dosing), 2, 5, 10, and 15. In addition, samples of blood were obtained from animals in Groups 1 and 3 on Study Day 20 and immediately prior to slaughter. Animals in Groups 1 and 2 were slaughtered 30 and 15 days after implantation, respectively, while animals in Group 3 (control) were slaughtered one day before those in Group 1. At slaughter, samples of liver, kidney, muscle, fat, and bile were obtained from each animal. Samples of urine and feces were collected on selected days from animals in Group 1 only. The total ^{14}C-content of each sample was determined either by a combustion method in conjunction with liquid scintillation counting or by direct liquid scintillation counting. In addition, concentrations of estradiol-17β in fat and muscle were determined by the method involving solid-phase extraction, high-performance liquid chromatographic (HPLC) separation and quantification by radioimmunoassay (RIA).

4. Results of the Study:

Since the implant is proposed for use in steers fed in confinement for slaughter, only residue data from steers are included in the summary table.

Tissue	Trenbolone acetate (ppb) Mean ± S.D.		Estradiol-17β (ppt) Mean ± S.D.	
	15 days	30 days	15 days	30 days
Liver	51.83 ± 12.47	85.23 ± 45.15	-.-	-.-
Kidney	14.25 ± 2.54	21.40 ± 9.25	-.-	-.-
Muscle	1.12 ± 0.42	1.99 ± 0.91	16.63 ± 2.85	24.43 ± 10.32
Fat	1.20 ± 1.29	1.41 ± 1.25	74.93 ± 20.71	95.23 ± 38.71

5. Statistical Analysis:

Because the tested dose was 1.5 times the marketed dose, the mean concentrations of trenbolone were compared to the published safe concentrations contained in 21 CFR 556.739 (50 ppb for muscle, 100 ppb for liver, 150 ppb for kidney, and 200 ppb for fat). Mean trenbolone residues were below the safe concentration for all of the sampled tissues and all of the sampled times. Mean trenbolone residues in liver at 15 and 30 days were not statistically different.

Mean concentrations of estradiol were compared to the allowable incremental increases permitted under 21 CFR 556.240 (120 ppt for muscle, 240 ppt for liver, 360 ppt for kidney, and 480 ppt for fat). Mean estradiol residues were below the allowable incremental increases for all of the sampled tissues at all of the sampled times.

D. Tolerance for Marker Residue

Since total residues of trenbolone in the tested edible tissues of steers are below the codified safe concentrations and not statistically different between Day 15 and Day 30, a marker residue is not required for trenbolone acetate.

Since residues of estradiol in the tested edible tissues of steers are below the allowable incremental increases, a marker residue is not required for estradiol benzoate.

E. Withdrawal Period

Since total residues of trenbolone in the tested edible tissues of steers are below the codified safe concentrations and residues of estradiol in the tested edible tissues are below the allowable incremental increases, a withdrawal period is not required.

F. Regulatory Method

Since a withdrawal period is not required for this approval, a regulatory analytical method likewise is not required.

7. 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 Synovex® Plus (ear implant contain 200 mg TBA and 28 mg EB) is safe and effective to improve feed efficiency in steers fed in confinement for slaughter, when used in accordance with its labeled conditions of use. Synovex® Plus was shown to provide improvement over each compound used alone, in compliance with 21 CFR 514.1(b)(8)(v).

Under section 512(c)(2)(F)(ii) 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 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.

8. LABELING

Five (5) pages of labeling are attached as follows:

1. Box label (front)
2. Box label (back)
3. Package Insert (front)
4. Package Insert (back)
5. Pouch Label