Approval Date: October 3, 2002

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-043

SYNOVEX® CHOICE (TRENBOLONE ACETATE AND ESTRADIOL BENZOATE) IMPLANTS

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

Sponsored by:

Fort Dodge Animal Health
Division of American Home Products Corp.
800 Fifth Street, NW
Fort Dodge, IA 50501

TABLE OF CONTENTS

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SYNOVEX® Choice (TRENBOLONE ACETATE AND ESTRADIOL BENZOATE) FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

1. General Information:

a. File Number:	NADA 141-043
b. Sponsor:	Fort Dodge Animal Heath Division of American Home Products 800 Fifth Street, NW Fort Dodge, Iowa 50501 Drug Labeler Code: 000856
c. Established Name:	Trenbolone Acetate and Estradiol Benzoate
d. Proprietary Name:	SYNOVEX® Choice
e. Dosage Form:	Implantation
f. How Supplied:	Implant made up of 4 pellets with each pellet containing 25 mg trenbolone acetate and 3.5 mg estradiol benzoate.
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	100 mg trenbolone acetate and 14 mg estradiol benzoate
i. Route of Administration:	Subcutaneous implant in the middle of the posterior aspect of the ear
j. Species/Class:	Cattle/Steers fed in confinement for slaughter
k. Recommended Dosage:	One implant containing 100 mg of trenbolone acetate and 14 mg estradiol benzoate. Each implant is made up of four pellets with each pellet containing 25 mg of trenbolone acetate and 3.5 mg estradiol benzoate.
l. Pharmacological Category:	Hormone
m. Indications:	For increased rate of weight gain in steers fed

	in confinement for slaughter.
n. Effect of Supplement:	Provides for the administration of a dose of 100 mg trenbolone acetate and 14 mg estradiol benzoate in steers fed in confinement for slaughter for increased weight gain. (Note: The sponsor currently has an approved ear implant containing 28 mg estradiol benzoate and 200 mg trenbolone acetate (Synovex® Plus™) – see 21 CFR 522.2478)

2. EFFECTIVENESS

The supplemental new animal drug application for Synovex® Choice 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 Section 1 above.

Pivotal Studies:

Dose Determination

A dose titration study was conducted at three sites using a uniform protocol such that the results could be pooled and summarized. The three sites were in major beef producing areas of the United States using management systems and diets typical of commercial feedlots.

Name and Address of Investigators:

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

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

Alvin Edwards, D.V.M., Ph.D.
Kansas State University
College of Veterinary Medicine
Manhattan, Kansas

Study Location: Lamar, Colorado

The purpose of this series of studies was to evaluate the dose response for estradiol benzoate (EB) and trenbolone acetate (TBA) on average daily gain of steers fed in confinement for slaughter. The test animals were crossbred 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, 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 and 183 days.

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

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

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 the EB/TBA implant on ADG. There was a significant ($P < .05$) dose effect on ADG with the response plateauing at a dose of 14 mg EB/100 mg TBA. The 14 mg EB/100 mg TBA dose was shown to be significantly ($P < .05$) better than controls, 300 mg TBA alone, and 60 mg EB alone. These data are sufficient to support the claims and dosage specified in Section 1. Because the improvement in ADG by steers treated with 28 mg EB/200 mg TBA was not significantly better than that by steers treated with 14 mg EB/100 mg TBA, the following disclaimer statement has been put on the label for Synovex Plus (28 mg EB/200 mg TBA:

> "Synovex Plus is not better for increased average daily gain than Synovex Choice (14 mg EB/100 mg TBA) in steers fed in confinement for slaughter."

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

EB/TBA (mg)	Location			Pooled Average
	Texas	**Colorado**	**California**	
0/0	2.26	3.41	3.10	2.93
0/300	2.53	3.66	2.96	3.06
60/0	2.65	3.66	3.36	3.23
14/100	2.89	3.87	3.38	3.38
28/200	2.82	3.86	3.59	3.43
42/300	2.87	4.08	3.59	3.52

The effects of treatment on yield grade, quality grade, marbling score, and liver abscess incidence were evaluated at slaughter. No effect of treatment was seen in yield grade or the incidence of liver abscesses. Compared to controls, carcasses from steers treated with the 28 mg EB/200 mg TBA and 14 mg EB/100 mg TBA implants exhibited decreased marbling scores (Table 2).

TABLE 2. SUMMARY FROM THREE DOSE TITRATION STUDIES COMPARING THE EFFECT OF VARIOUS LEVELS OF TRENBOLONE ACETATE AND ESTRADIOL BENZOATE ON MARBLING SCORES IN FEEDLOT STEERS

EB/TBA (mg)	**LS-means for Marbling Score (standard error = 0.1053)**	**P-value for one-sided comparison to control**
0/0	4.32	-
0/300	4.16	0.1301
60/0	4.01	0.0216
14/100	4.06	0.0391
28/200	3.88	0.0039
42/300	3.87	0.0035

Because of this observed decrease in marbling scores, the following statement is required on the label for the:

a) 8 pellet, 28 mg EB/200 mg TBA dose (Synovex® Plus™).

"Studies have demonstrated that the administration of Synovex Plus can result in decreased marbling scores when compared to non-implanted steers."

b) 4 pellet, 14 mg EB/100 mg TBA dose (Synovex® Choice).

"Studies have demonstrated that the administration of Synovex Choice can result in decreased marbling scores when compared to non-implanted steers."

3. TARGET ANIMAL SAFETY

The supplemental new animal drug application for Synovex® Choice references the target animal safety studies summarized in the FOI for NADA 141-043 (61 FR 14482-April 2, 1996, as amended at 61 FR 29479-June 11, 1996). The data from those studies demonstrate the safety of the new animal drug for the indications for use and dosage as given in Sections 1 and 2 above.

4. HUMAN SAFETY

- Toxicity:

  The toxicity studies summarized in the FOI under NADA 141-043 (61 FR 14482-April 2, 1996, as amended at 61 FR 29479-June 11, 1996) have met the agency's requirement for human food safety for trenbolone acetate.

- Acceptable Daily Intake

  The Acceptable Daily Intake (ADI) for total residues of trenbolone is 0.4 ug/kg/day (64 FR 18573).

- Allowable Incremental Increases

  Allowable incremental increases of estradiol ($E_2\beta$) have been established by the agency under 21 CFR 556.240. 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.

- Residue Depletion Studies

  The residue depletion study is summarized in the FOI Summary for NADA 141-043 (61 FR 14482-April 2, 1996, as amended at 61 FR 29479-June 11, 1996).

- Tolerance

  A tolerance for total trenbolone residues in uncooked edible tissues of cattle is not needed.

- Withdrawal Time

  As summarized in the FOI for NADA 141-043 (61 FR 14482-April 2, 1996, as amended at 61 FR 29479-June 11, 1996) a withdrawal period is not required.

- Regulatory Method

  SYNOVEX® Choice qualifies for a zero withdrawal and, as such, a regulatory analytical method for residues is not required.

5. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrates that an implant containing 100 mg trenbolone acetate and 14 mg estradiol benzoate when administered to steers fed in confinement for slaughter is safe and effective for the claim of increased rate of weight gain.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the layman have been provided and the product will retain its over-the-counter marketing status.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the use of the product (SYNOVEX® Choice); containing 100 mg trenbolone acetate and 14 mg estradiol benzoate for which this supplement is approved.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change. 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.

6. ATTACHMENTS

Facsimile labeling for each product are attached as indicated below:

SYNOVEX® Choice
1. Pouch Panel (front)
2. Pouch Panel (back)
3. Folding Carton
4. Folding Carton (front panel and bottom flap)
5. Folding Carton (back panel)
6. Folding Carton (page 1 fold-out section)
7. Folding Carton (page 2 fold-out section and bottom flap)

SYNOVEX® Plus
1. Pouch Panel (front)
2. Pouch Panel (back)
3. Folding Carton
4. Folding Carton (front panel and bottom flap)
5. Folding Carton (back panel)
6. Folding Carton (side panel #1)
7. Folding Carton (side panel #2)
8. Folding Carton (page 1 fold-out section)
9. Folding Carton (page 2 fold-out section and bottom flap)