Date of Approval: December 19, 2024

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-043

SYNOVEX Choice® and SYNOVEX® PRIMER™ [1]

(trenbolone acetate and estradiol benzoate implants)

Growing beef steers and heifers on pasture (stocker, feeder, and slaughter)

This supplement provides for the approval of a new indication for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) to SYNOVEX Choice®; and provides for the approval of a new indication for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) to SYNOVEX® PRIMER™.

Sponsored by:

Zoetis Inc.

[1] This supplemental approval applies to the single use of either SYNOVEX Choice® or SYNOVEX® PRIMER™ for the stated indication and target animal.

Executive Summary

SYNOVEX Choice® and SYNOVEX® PRIMER™ (trenbolone acetate and estradiol benzoate implants) are approved for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter). The implant is placed subcutaneously in the middle one-third of the back of the ear, between the skin and the cartilage, using a SYNOVEX® applicator. The implant is for single use only and dissolves slowly under the skin and does not need to be removed later. The ears of treated cattle are not used for human food.

The Food and Drug Administration (FDA) approved both types of implants as over-the-counter drugs. Each SYNOVEX Choice® implant contains 100 mg trenbolone acetate and 14 mg estradiol benzoate. Each SYNOVEX® PRIMER™ implant contains 50 mg of trenbolone acetate and 7 mg estradiol benzoate. Trenbolone and estradiol are steroid hormones that act by redirecting how nutrients are used by the animal, resulting in increased muscle growth and weight gain in castrated male beef cattle (steers) and non-pregnant beef cattle (heifers).

Safety and Effectiveness

The sponsor conducted a multi-site field study to show that SYNOVEX Choice® and SYNOVEX® PRIMER™ increase average daily weight gain (ADG) in growing beef steers and heifers on pasture (stocker, feeder, and slaughter—see Appendix III of Guidance for Industry #191 for definitions of these subsets of growing beef steers and heifers on pasture[2]).

The field study enrolled young, healthy cattle of mixed English and Continental European beef breeds at four sites throughout the United States (U.S.). The sites represented typical management practices and forage types for pasture beef cattle in different regions of the U.S. Cattle at two sites grazed on irrigated pastures, and cattle on the other two sites grazed on dryland pasture.

On Day 0, all cattle were individually weighed and then implanted with either SYNOVEX Choice® or SYNOVEX® PRIMER™ or were sham-implanted (an empty implant needle was inserted). At each site, cattle from both treated groups and the control group were comingled within each pasture. The cattle were individually weighed again on the final day of the study (Day 90).

Over the study period and across sex and study site, cattle in the two treated groups had a greater ADG than cattle in the control group (1.49 and 1.43 lb of weight gain per day for SYNOVEX Choice® and SYNOVEX® PRIMER™, respectively, compared to 1.29 lb of weight gain per day for the control group). Adverse reactions at the implant site (swelling or scar tissue) were uncommon and seen in all treatment groups. The abnormal health events observed during the study (mainly pink eye, foot rot, respiratory disease, and lameness) were typical for pasture beef cattle.

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[2] The Center for Veterinary Medicine (CVM) Guidance for Industry (GFI) #191 Changes to Approved NADAs – New NADAs vs. Category II Supplemental NADAs (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-191-changes-approved-nadas-new-nadas-vs-category-ii-supplemental-nadas). See also Classes of Major Food-Producing Animals for New Animal Drug Applications (https://www.fda.gov/animal-veterinary/new-animal-drug-applications/classes-major-food-producing-animals-new-animal-drug-applications).

FDA did not require the sponsor to conduct new target animal safety studies for this supplemental approval. Target animal safety was supported by the target animal safety information for previous approvals of SYNOVEX PLUS® under New Animal Drug Application (NADA) 141-043. SYNOVEX PLUS® is a higher-dose implant of trenbolone acetate and estradiol benzoate in growing beef steers and heifers fed in confinement for slaughter. Target animal safety information was also evaluated in the multi-site field study described above. The study did not raise any animal safety concerns. Bulling behavior (excessive mounting by other cattle) and other sexual disorders (vaginal or rectal prolapse and preputial edema) were not observed at any of the sites during the field study. However, the labeling for SYNOVEX Choice® and SYNOVEX® PRIMER™ will continue to include animal safety warnings that bulling has been occasionally reported in implanted steers and heifers; and vaginal and rectal prolapse, udder development, ventral edema, and elevated tailheads have occasionally been reported in implanted heifers.

The safety and effectiveness of SYNOVEX Choice® and SYNOVEX® PRIMER™ have not been evaluated in beef calves less than 2 months of age, dairy calves, and veal calves; in cattle intended for subsequent breeding; or in dairy cows. Therefore, the drugs cannot be used in these groups of animals.

SYNOVEX Choice® and SYNOVEX® PRIMER™ are not approved for repeated implantation (reimplantation) with this or any other cattle ear implant in growing beef steers and heifers on pasture or in a dry lot as the safety and effectiveness of reimplantation have not been evaluated.

Human Food Safety
FDA evaluated the need to address the impact of trenbolone acetate and estradiol benzoate on antimicrobial resistance among bacteria of public health concern in or on beef steers and heifers treated with SYNOVEX Choice® or SYNOVEX® PRIMER™. The drugs 1) do not have properties that exert selection pressure for the development of resistant bacteria in food-producing animals; 2) are not used to treat gastroenteritis or other bacterial diseases in people; 3) are not being developed to treat a bacterial disease in people; and 4) are not used to treat a bacterial disease in food-producing animals. Therefore, FDA determined that a microbial food safety assessment was not required for the intended use of SYNOVEX Choice® and SYNOVEX® PRIMER™.

FDA determined that it was not necessary to reassess the acceptable daily intake (ADI) for total residue of trenbolone. FDA previously established the ADI for total residue of trenbolone as 0.4 µg/kg of body weight per day and the safe concentrations in individual edible tissues of cattle as 80 parts per billion (ppb) for muscle, 240 ppb for liver, 480 ppb for kidney, and 480 ppb for fat.

FDA regulates estradiol on the basis of allowable incremental increases, meaning estradiol residues are not allowed to be higher than a certain increment above the naturally occurring estradiol concentrations in untreated cattle. The agency determined that it was not necessary to reassess the allowable incremental increases of estradiol which are as follows: 0.2 ppb for muscle, 0.6 ppb for liver, 1.2 ppb for kidney, and 1.2 ppb for fat.

FDA did not require the sponsor to conduct new residue chemistry studies for this supplemental approval. For both SYNOVEX Choice® and SYNOVEX® PRIMER™, the withdrawal period remains zero days. Tolerances for trenbolone and estradiol are not required; therefore, an official analytical method for monitoring their residues in cattle is not required.

Conclusions

Based on the data submitted by the sponsor for the approval of SYNOVEX Choice® and SYNOVEX® PRIMER™, FDA determined that the drugs are safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-043

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

SYNOVEX Choice® and SYNOVEX® PRIMER™

D. Drug Product Established Name

trenbolone acetate and estradiol benzoate implants

E. Pharmacological Category

Steroid hormone

F. Dosage Form

Implants

G. Amount of Active Ingredient

SYNOVEX Choice®: One implant contains 100 mg of trenbolone acetate and 14 mg of estradiol benzoate. Each implant consists of 4 pellets.

SYNOVEX® PRIMER™: One implant contains 50 mg of trenbolone acetate and 7 mg of estradiol benzoate. Each implant consists of 2 pellets.

H. How Supplied

One pouch contains 10 cartridges. Each cartridge contains 10 implants (100 implants total).

I. Dispensing Status

Over the counter (OTC)

J. Dosage Regimen

SYNOVEX Choice®: Administer one SYNOVEX Choice® implant (four pellets), containing 100 mg of trenbolone acetate and 14 mg of estradiol benzoate, to each steer or heifer by subcutaneous implantation in the middle-third of the ear.

SYNOVEX® PRIMER™: Administer one SYNOVEX® PRIMER™ implant (two pellets), containing 50 mg of trenbolone acetate and 7 mg of estradiol benzoate, to each steer or heifer by subcutaneous implantation in the middle-third of the ear.

K. Route of Administration

Subcutaneous

L. Species/Classes

Growing beef steers and heifers on pasture (stocker, feeder, and slaughter)

M. Indication

For increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter).

N. Effect of Supplement

This supplement provides for the approval of a new indication for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) to SYNOVEX Choice®; and provides for the approval of a new indication for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) to SYNOVEX® PRIMER™.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage for SYNOVEX Choice® or for SYNOVEX® PRIMER™. The FOI Summaries for the supplemental approvals of NADA 141-043 dated October 3, 2002, and August 3, 2014, for SYNOVEX Choice® contain dosage characterization information for increased rate of weight gain in growing beef steers and heifers fed in confinement for slaughter. The FOI Summary for the supplemental approval of NADA 141-043 dated April 5, 2024, for SYNOVEX Choice® and for SYNOVEX® PRIMER™, contain studies that characterize the dosage for increased rate of weight gain in growing beef steers and heifers in a dry lot for both products.

B. Substantial Evidence

1. Dosage Confirmation Study

Title: Efficacy of Synovex Choice and Synovex PD for Increased Rate of Weight Gain in Growing Beef Steers and Heifers on Pasture. (Study No. A131C-US-21-928)

Study Dates: May 1, 2023, to March 8, 2024

Study Locations: This multi-location, randomized, negative control study was conducted at four sites in the U.S.: Madera, CA; Parma, ID; Grass Range, MT; and Manhattan, KS.

Study Design:

Objective: To evaluate the effectiveness and field safety of SYNOVEX® PRIMER™ and SYNOVEX Choice®, both for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter).

Study Animals: The study enrolled 70 steers and 70 heifers per treatment at each of the 4 sites for a total of 1,680 head of cattle (840 steers and 840 heifers). Cattle were mixed English and Continental European beef breeds and were approximately 5 to 9 months of age. Cattle weighed between 334 and 778 lb on Day 0 of the study. Animals were sourced from regional ranches or producers (California, Montana, and Kansas) or from their own herd (Idaho). At arrival, cattle were weighed, examined for health status, vaccinated, and treated for internal and external parasites. Ears were palpated for existing implants and any implants found were removed. Steers were examined for castration. Heifers were considered pre-pubertal and were not examined for pregnancy. Cattle were acclimated at each study site in pastures or a dry lot for a minimum of 21 days (ranging from 21 to 43 days) prior to Day 0 of the study.

Animal Housing and Management: Study animals at each site were housed and managed on pastures representing typical management practices and forage types for pasture beef cattle in different regions in the U.S. Two sites (Sites A and B) grazed on irrigated pastures, ranging in size from 39 to 45 acres. Two sites (Sites C and D) grazed dryland pastures, ranging in size from 273 to 1,194 acres. Site B strip grazed within each of their four pastures while the remaining three sites grazed cattle on treatment pastures for the duration of the treatment phase without rotating pastures. All animals had *ad libitum* access to water. Pastures were deemed sufficient for *ad libitum* intake at the beginning of the study, with feeding of a supplement (protein/concentrate) permitted if necessary. The amount of supplement was determined by the site nutritionists based on visual inspection of cattle, quality of sampled forage, and to target an average daily gain (ADG) of 1.5 to 2.5 lb per day. Supplemental feed was offered at Sites A, C, and D. At the end of the study, animals were returned to the study site herd. A summary of key dates at each location is in Table II.1.

Table II.1. Summary of Site Locations and the Study Dates and Study Days for the Live Phase Portion of the Study.

Site	Day 0	Day 40	Day 90
A (CA)	July 13, 2023	August 22, 2023 (Study Day 40)	October 11, 2023 (Study Day 90)
B (ID)	June 2, 2023	July 12, 2023 (Study Day 40)	August 30, 2023 (Study Day 89)
C (MT)	July 7, 2023	August 16, 2023 (Study Day 40)	October 5, 2023 (Study Day 90)
D (KS)	May 25, 2023	July 6, 2023 (Study Day 42)	August 28, 2023 (Study Day 95)

Experimental design: This was a randomized, negative control study replicated across four locations.

Pastures were randomly assigned to sex with two pastures assigned to each sex at each site. Steers were randomly assigned to steer pastures and heifers were randomly assigned to heifer pastures. Three treatments were then randomly assigned to animals within pasture (and sex): sham negative control; SYNOVEX® PRIMER™; or SYNOVEX Choice®; in a 1:1:1 ratio.

Negative controls were sham implanted using an empty implant needle. Cattle from all treatment groups were comingled within each pasture, with steers and heifers housed on separate pastures. All personnel at each site were masked except the treatment administrator and their assistant. The study was conducted according to Guidance for Industry #85 (VICH GL9) Good Clinical Practices.

Drug Administration: On the day of enrollment (Day 0), animals were implanted with either SYNOVEX® PRIMER™, SYNOVEX Choice®, or were sham implanted (negative control) in the middle third of the back of the ear using a SYNOVEX® SX10 applicator according to the randomization plan. One SYNOVEX Choice® animal erroneously received two implants and was excluded from the data analysis for the primary effectiveness variable (ADG).

Measurements and Observations:

Individual body weights (BW) of study animals were collected at the pre-treatment evaluation (Days -3, -2 or -1), Day 0, the interim Day 40 timepoint, and the final Day 90 timepoint. Animals removed from the study early were weighed at time of removal and their weights used in the analysis.

All cattle were observed daily for health abnormalities. Any illnesses or injuries were recorded, and any treatments were documented. Animals that died during the study were necropsied, if possible, to determine cause of death.

On the interim Day 40 timepoint, ears were examined for reactions (swelling, hardness, or abscesses) and to confirm implant retention. Ear evaluations were also performed on animals removed from the study prior to the scheduled exam.

Statistical Methods:

The effectiveness variable, ADG, was calculated using the following formula:

$$\text{ADG} = \frac{(\text{Final animal weight} - \text{Initial animal weight})}{\text{Total number of animal days}}$$

Final animal weight is the BW measured at the final Day 90 timepoint or early removal day. Initial animal weight is the BW measured on Day 0. Total number of animal days equals the sum of days each animal was on study.

A total of 23 animals (13 steers and 10 heifers) did not complete the study, 21 for health reasons and 2 for protocol deviations. Five animals (2 steers and 3 heifers) died, and 18 animals (11 steers and 7 heifers) were removed from study before its completion. All animals were retained in the databases for evaluation of safety parameters. The data on deaths and removals were summarized by treatment across sex. Analysis of general health observations are discussed in Section III. Target Animal Safety.

Nine animals (four steers and five heifers) were excluded from the data analysis for the primary effectiveness variable (ADG) due to protocol deviations or health issues. Data from all four sites were pooled and ADG was analyzed using a general linear mixed model with the fixed effects of treatment, sex, and treatment-by-sex interaction. The random effects were site, pasture within site and sex, site-by-treatment interaction, site-by-sex interaction, and site-by-treatment-by-sex interaction. The sex-by-treatment interaction was not significant (P=0.0768), so heifer and steer data were pooled together for analysis. Success criteria were based on significant improvement in ADG over the duration of the study (from Day 0 to the final Day 90 timepoint or early removal day) with each implant group compared to the sham implanted control group.

Results:

The analysis results of ADG (lb/d) from Day 0 to the final Day 90 timepoint or early removal day by treatment across sex are listed in Table II.2 below. The final analysis for ADG included 1,671 animals (836 steers and 835 heifers). The overall least squares mean (LSM) of ADG for animals treated with SYNOVEX® PRIMER™ was significantly different and greater compared to sham-implanted animals (P=0.0014; 1.43 vs. 1.29 lb/d). The overall LSM of ADG for animals treated with SYNOVEX Choice® was significantly different and greater compared to sham-implanted animals (P=0.0007; 1.49 vs. 1.29 lb/d).

Table II.2. Summary of Animal Body Weight (BW) and Analysis of Average Daily Gain (ADG) from Day 0 to the Final Day 90 Timepoint or Early Removal Day Across Sex and Site.

Treatment	Number of Animals	Initial BW (lb), Mean (SD)	Final BW (lb), Mean (SD)	LSM of ADG[1] (lb/d)	SE	*P*-value[2]
Negative Control	558	568.3 (78.97)	685.1 (105.55)	1.29	0.208	-
SYNOVEX® PRIMER™	557	566.5 (78.50)	696.6 (105.92)	1.43	0.208	0.0014
SYNOVEX Choice®	556	565.5 (78.55)	701.9 (109.45)	1.49	0.209	0.0007

SD = Standard Deviation, LSM = Least Squares Mean, SE = Standard Error
[1] Fixed effects *P*- values: Treatment, *P*=0.0007; Sex, *P*=0.1643; Treatment × Sex, *P*=0.0768.
[2] Multiple Comparison Adjustment- Hochberg Procedure

Abnormal health events were typical for pasture beef cattle. A total of 331 animals had an abnormal health event, or 19.7% of all enrolled animals (331/1680). Most abnormal health events were due to infectious bovine keratoconjunctivitis (commonly known as pink eye), occurring in 272 animals primarily at Sites B and D. These eye disorders were significantly greater in SYNOVEX® PRIMER™ treated cattle compared to control (18.2% vs. 14.1%, unadjusted *P*=0.0378). This was considered due to chance and unrelated to treatment as no increase in events were observed in SYNOVEX Choice® treated cattle compared to control (*P*=0.2785). The other abnormal health events that occurred in more than one animal were skin and appendage conditions (primarily foot rot), respiratory conditions, and musculoskeletal (lameness). A summary of all abnormal health events is in Table II.3 below.

Table II.3. Summary of Abnormal Health Events

Disorder	Control n (%)*	SYNOVEX® PRIMER™ n (%)*	SYNOVEX Choice® n (%)*	*Total across Treatments n*
Digestive Tract	0 (0.0%)	1 (0.2%)	1 (0.2%)	*2*
Eye	79 (14.1%)	102 (18.2%)	91 (16.3%)	*272*
Musculoskeletal	2 (0.4%)	3 (0.5%)	3 (0.5%)	*8*
Respiratory	5 (0.9%)	6 (1.1%)	7 (1.3%)	*18*
Skin and Appendage	8 (1.4%)	8 (1.4%)	12 (2.1%)	*28*
Mammary Gland	1 (0.2%)	0 (0.0%)	0 (0.0%)	*1*
Systemic	0 (0.0%)	2 (0.4%)	0 (0.0%)	*2*
Total across disorders	*95*	*122*	*114*	*331*

n = number of animals affected.
*Percentages based on 560 total animals per treatment group. One SYNOVEX Choice® animal erroneously received two implants.

Abnormal health events generally resolved. Of the 1,680 animals on the study, 21 animals did not complete the study due to severe illness or injury (16) or death (5) prior to the end of the study. Of these 21 animals, 5 were in the control group, 8 were in the SYNOVEX® PRIMER™ treatment group, and 8 were in the SYNOVEX Choice® treatment group. There was no significant effect of treatment on the incidence of deaths and removals.

Adverse Reactions:

Adverse reactions at the implant sites were uncommon. Implant reactions were detected in all treatment groups and were described as swelling or scar tissue. A summary of implant site reactions is in Table II.4 below.

Table II.4. Frequency of Implant Reactions at the Interim Day 40 Timepoint Across Sex by Site.

Treatment	Site A (CA) n/N (%)	Site B (ID) n/N (%)	Site C (MT) n/N (%)	Site D (KS) n/N (%)	Overall n/N (%)
Negative Control	1/140 (0.7%)	2/139 (1.4%)	0/139 (0.0%)	0/137 (0.0%)	3/555 (0.5%)
SYNOVEX® PRIMER™	2/140 (1.4%)	0/138 (0.0%)	0/138 (0.0%)	1/138 (0.7%)	3/554 (0.5%)
SYNOVEX Choice®	3/139 (2.2%)	0/138 (0.0%)	3/138 (2.2%)	0/138 (0.0%)	6/553 (1.1%)
Overall	6/419 (1.4%)	2/415 (0.5%)	3/415 (0.7%)	1/413 (0.2%)	12/1662 (0.7%)

n = number of animals with an implant reaction, N = number of animals observed.

Conclusions: The study demonstrated substantial evidence of effectiveness for the following indications:

SYNOVEX Choice®: for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter).

SYNOVEX® PRIMER™: for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter).

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summaries for the supplemental approvals of NADA 141-043 dated October 3, 2002, August 3, 2014, and April 5, 2024, for SYNOVEX Choice®, and the FOI Summary for the supplemental approval of NADA 141-043 dated April 5, 2024, for SYNOVEX® PRIMER™, relied on information used for previous original and supplemental approvals of NADA 141-043 for SYNOVEX PLUS®, an 8-pellet implant that contains 200 mg of trenbolone acetate and 28 mg of estradiol benzoate. SYNOVEX Choice® and SYNOVEX® PRIMER™ use identical pellets. SYNOVEX Choice® is a 4-pellet implant that contains 100 mg of trenbolone acetate and 14 mg of estradiol benzoate and

SYNOVEX® PRIMER™ is a 2-pellet implant that contains 50 mg of trenbolone acetate and 7 mg of estradiol benzoate.

The FOI Summaries for the original approval of NADA 141-043 dated February 22, 1996, and supplemental approval dated September 30, 1998, contain summaries of target animal safety studies for growing beef steers and heifers fed in confinement for slaughter for SYNOVEX PLUS®. Steers and heifers were implanted with 1, 3, or 5 implants or an empty needle (negative control) on day 0. The 5x group received 1,000 mg trenbolone acetate and 140 mg estradiol benzoate. There were no adverse effects on animal health, clinical pathology parameters, or in gross pathologic findings at any dose level.

The safety of SYNOVEX Choice® and SYNOVEX® PRIMER™ in growing beef steers and heifers in pasture conditions was evaluated under intended conditions of use in a multi-location field study, as described in Section II. Effectiveness. As noted in that section, abnormal health events were typical for pasture beef cattle: pink eye, foot rot, respiratory disease, and lameness. The incidence of these events was less than or consistent with the incidence typically seen under commercial conditions. Only eye disorders were significantly greater in the SYNOVEX® PRIMER™ treatment group compared to control; however, this was considered due to chance and unrelated to treatment as no increase in events were observed in the higher-dosed SYNOVEX Choice® treated cattle compared to control. Most cases of pink eye occurred at two locations and occurred across all treatment groups. Abnormal health events generally resolved; however, 21 animals, representing 1.25% of animals on study (21/1680) were removed due to severe illness or injury (16/1680) or died (5/1680) prior to the end of the study. There was no significant effect of treatment on the incidence of deaths and removals. Bulling/riding behavior and other sexual disorders (vaginal or rectal prolapse, preputial edema) were not observed at any of the sites during the effectiveness study, but the labeling for SYNOVEX Choice® and SYNOVEX® PRIMER™ will continue to include warnings that bulling has been occasionally reported in implanted steers and heifers; vaginal and rectal prolapse, udder development, ventral edema and elevated tailheads have occasionally been reported in heifers administered these implants.

Because safety and effectiveness of SYNOVEX Choice® has not been evaluated in the following classes, labeling prohibits its use as follows:

- In beef calves less than 2 months of age, dairy calves, and veal calves.
- In animals intended for subsequent breeding, or in dairy cows.
- Other than as described on the labeling, this implant is not approved for repeated implantation (reimplantation) with any other cattle ear implant in growing beef steers and heifers fed in confinement for slaughter, on pasture, or in a dry lot.

Because safety and effectiveness of SYNOVEX® PRIMER™ has not been evaluated in the following classes, labeling prohibits its use as follows:

- In beef calves less than 2 months of age, dairy calves, and veal calves.
- In animals intended for subsequent breeding, or in dairy cows.
- For repeated implantation (reimplantation) with this or any other cattle ear implant in growing beef steers and heifers on pasture or in a dry lot.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

The Agency evaluated the need to address the impact of the use of trenbolone acetate and estradiol benzoate on antimicrobial resistance among bacteria of public health concern in or on trenbolone acetate and estradiol benzoate-treated beef steers and heifers. After reviewing information (literature, data, etc.) both submitted by the sponsor and available in the public domain, the Agency determined:

- Trenbolone acetate and estradiol benzoate are not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,
- Trenbolone acetate and estradiol benzoate are not used to treat gastroenteritis or other bacterial diseases in humans,
- Trenbolone acetate and estradiol benzoate (or a similar class representative) are not under development to treat a bacterial disease in humans, and
- Trenbolone acetate and estradiol benzoate are not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined that a microbial food safety assessment was not required for this approved use of trenbolone acetate and estradiol benzoate in beef steers and heifers.

B. Toxicology

Trenbolone

The codified Acceptable Daily Intake (ADI) for total residue of trenbolone is 0.4 µg/kg of body weight per day, as listed under 21 CFR §556.739. Reassessment of the codified ADI was not needed for this supplemental approval.

Based on the codified ADI of 0.4 µg/kg of body weight per day and revised food consumption values of 300 g (muscle), 100 g (liver), 50 g (kidney) and 50 g (fat), the safe concentrations for total residues of trenbolone in edible tissues are: 80 parts per billion (ppb) for muscle, 240 ppb for liver, 480 ppb for kidney, and 480 ppb for fat.

The FOI Summaries for the original approval of NADA 141-043, dated February 22, 1996, and the supplemental approval, dated September 30, 1998, contain summaries of all toxicology studies and information.

Estradiol

Residues of estradiol are regulated on the basis of the codified allowable incremental increases (21 CFR §556.240). Residues of estradiol are not permitted in excess of the following increments above the concentrations of estradiol naturally present in untreated cattle: 0.2 ppb for muscle, 0.6 ppb for liver, 1.2 ppb for kidney and 1.2 ppb for fat.

C. Residue Chemistry

CVM did not require new residue chemistry studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-043 dated February 22, 1996, and supplemental approvals dated September 30, 1998, October 3, 2002, August 3, 2014, and April 5, 2024, contain summaries of residue chemistry studies/information for cattle.

This supplement does not result in any changes to the previously established withdrawal period. The withdrawal period remains zero days. Refer to the FOI Summaries for NADA 141-043 dated February 22, 1996, September 30, 1998, October 3, 2002, August 3, 2014, and April 5, 2024.

D. Analytical Method for Residues

Because a tolerance is not required for either trenbolone or estradiol residues in cattle, an official analytical method for either trenbolone or estradiol residues in cattle is not required. See the FOI Summaries for NADA 141-043, dated February 22, 1996, September 30, 1998, October 3, 2002, August 3, 2014, and April 5, 2024.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SYNOVEX Choice® and SYNOVEX® PRIMER™:

Not for use in humans. Keep out of reach of children.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that SYNOVEX Choice® and SYNOVEX® PRIMER™, when used according to the label, are safe and effective for the effect of supplement in the General Information Section above. Additionally, data demonstrate that residues in food products derived from growing beef steers and heifers on pasture (stocker, feeder, and slaughter) treated with SYNOVEX Choice® and SYNOVEX® PRIMER™ will not represent a public health concern when the product is used according to the label.

A. Marketing Status

These products can be marketed OTC because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the labeling are reasonably certain to be followed in practice.

B. Exclusivity

This supplemental approval for SYNOVEX Choice® and SYNOVEX® PRIMER™ qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to SYNOVEX Choice® for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter); and to SYNOVEX® PRIMER™

for increased rate of weight gain in growing beef steers and heifers on pasture (stocker, feeder, and slaughter).

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval required a reevaluation of certain safety or effectiveness data in the application.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.