Date of Approval: October 29, 2021

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-348

SYNOVEX® ONE Grower

trenbolone acetate and estradiol benzoate
extended-release implants

Extended-release implants

Growing beef steers and heifers fed in confinement for slaughter

This supplement provides for approval of the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

Sponsored by:

Zoetis Inc.

Executive Summary

SYNOVEX® ONE Grower (trenbolone acetate and estradiol benzoate extended-release implants) is approved for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter ("feedlot" beef cattle). 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 dissolves slowly under the skin and does not need to be removed later. The ears of treated cattle are not used for human food.

FDA previously approved this product for increased rate of weight gain for up to 200 days in growing beef steers and heifers on pasture (stocker, feeder, and slaughter). It was marketed as SYNOVEX® ONE Grass but will now be renamed SYNOVEX® ONE Grower. SYNOVEX® ONE Grower is for use in growing beef steers and heifers both on pasture and in feedlots.

Proprietary Name	Established Name	Application Type and Number	Sponsor
SYNOVEX® ONE Grower	trenbolone acetate and estradiol benzoate extended-release implants	New Animal Drug Application (NADA) 141-348	Zoetis Inc.

Each SYNOVEX® ONE Grower implant contains six pellets, with each pellet containing 25 mg trenbolone acetate and 3.5 mg estradiol benzoate in an extended-release coating (for a total of 150 mg trenbolone acetate and 21 mg estradiol benzoate per implant). The implant slowly releases the two hormones over time. Trenbolone is a synthetic version of the natural androgen testosterone. Estradiol is a naturally-occurring estrogen. Both hormones 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 heifers.

FDA approved SYNOVEX® ONE Grower as an over-the-counter drug because the agency determined that adequate "directions for use" can be written on the labeling in such a way that non-veterinarians can use the drug safely and effectively.

Safety and Effectiveness

The sponsor conducted a multi-site field effectiveness study to show that SYNOVEX® ONE Grower increases average daily weight gain (ADG) in feedlot beef cattle. The sites were located throughout the U.S. with a range of management and environmental conditions that are representative of the U.S. beef cattle feedlot industry. Healthy purebred or crossbred English or Continental beef steers and heifers were sourced from livestock auctions or ranches from major beef cattle-producing regions of the U.S.

On Day 0, all cattle were individually weighed and then given a single SYNOVEX® ONE Grower implant or were sham-implanted (the implant needle was inserted with no delivery). The cattle were individually weighed again on the final day of the study, which varied across sites from 200 to 204 days after implantation.

Over the study period, and regardless of sex or study site, cattle in the treated group had a greater ADG than cattle in the control group (3.16 pounds of weight gain per day compared to 2.85 pounds of weight gain per day, respectively). Adverse reactions at the implant site were uncommon. The abnormal health events observed during the study (mainly pneumonia, ruminal bloat, foot rot, and coccidiosis) occurred in both treated and control groups and at a frequency typical for these common conditions of U.S. feedlot beef cattle.

The sponsor used models to estimate the effects of SYNOVEX® ONE Grower on carcass quality of growing beef steers and heifers. The models predicted that the effects on carcass quality would be similar to those seen for SYNOVEX® ONE Feedlot (a higher-dose implant of trenbolone acetate and estradiol benzoate also approved under NADA 141-348). Therefore, the labeling for SYNOVEX® ONE Grower contains a similar statement to the labeling for SYNOVEX® ONE Feedlot regarding carcass quality: "NOTE: The administration of SYNOVEX® ONE Grower may result in decreased marbling scores when compared to non-implanted steers and heifers."

FDA did not require the sponsor to conduct new target animal safety studies for this supplemental approval. Target animal safety was supported by the following:

- Target animal safety information for previous approvals of SYNOVEX® Plus (NADA 141-043), which is a higher-dose implant of trenbolone acetate and estradiol benzoate in growing beef steers and heifers fed in confinement for slaughter;
- Pharmacovigilance information for the currently approved use of SYNOVEX® ONE Grass (NADA 141-348) in growing beef steers and heifers on pasture (this product is now named SYNOVEX® ONE Grower);
- Pharmacovigilance information for the currently approved use of the higher-dose SYNOVEX® ONE Feedlot (NADA 141-348) in growing beef steers and heifers fed in confinement for slaughter; and
- Target animal safety information evaluated in the field effectiveness study described above. The study did not raise any animal safety concerns.

Taken together, this information supports the target animal safety of SYNOVEX® ONE Grower in growing beef steers and heifers fed in confinement for slaughter.

The labeling for SYNOVEX® ONE Grower includes animal safety warnings that bulling behavior (excessive mounting by other cattle) has occasionally been reported in implanted steers and heifers; and that vaginal and rectal prolapse, udder development, ventral edema, and elevated tailheads have occasionally been reported in implanted heifers.

The safety and effectiveness of SYNOVEX® ONE Grower have not been evaluated in beef calves less than 2 months of age, dairy calves, and veal calves; in cattle intended for breeding; or in dairy cows. Therefore, the labeling for SYNOVEX® ONE Grower prohibits the use of the product in these groups of animals. In addition, SYNOVEX® ONE Grower is only approved for one implantation in the pasture stage and one in the feedlot stage. Therefore, the labeling for SYNOVEX® ONE Grower prohibits more than one implantation during each stage of growth (pasture and feedlot).

Human Food Safety

FDA conducted a human food safety assessment to ensure that any residues of trenbolone acetate and estradiol benzoate in the edible tissues of treated cattle are at a concentration that present a reasonable certainty of no harm to people when SYNOVEX® ONE Grower is used according to the labeling. The human food safety evaluation is conducted from the perspectives of microbial food safety, toxicology, and residue chemistry.

For microbial food safety, FDA reviewed information submitted by the sponsor and also information that was publicly available regarding the impact of SYNOVEX® ONE Grower on antimicrobial resistance among bacteria of public health concern. The drug 1) does not exert selection pressure for the development of resistant bacteria in food-producing animals; 2) it is not used to treat gastroenteritis or other bacterial diseases in people; 3) the drug class is not being developed to treat a bacterial disease in people; and 4) it is not used to treat a bacterial disease in food-producing animals. Therefore, FDA determined the sponsor did not need to provide additional information regarding microbial food safety for the approved use of SYNOVEX® ONE Grower in growing beef steers and heifers fed in confinement for slaughter.

FDA determined that it was not necessary to reassess the acceptable daily intake (ADI) and safe concentrations 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 allowable incremental increases of estradiol are 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. 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® ONE Grower, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-348

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

SYNOVEX® ONE Grower

D. Drug Product Established Name

trenbolone acetate and estradiol benzoate extended-release implants

E. Pharmacological Category

Steroid hormone

F. Dosage Form

Extended-release implants

G. Amount of Active Ingredients

One implant contains 150 mg of trenbolone acetate and 21 mg of estradiol benzoate with a porous polymer film coating that extends the pay-out period of the final formulation up to 200 days. Each implant consists of 6 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

Administer complete contents of one cartridge cell (one implant) to each steer or heifer by subcutaneous implantation in the middle one-third of the ear using a Synovex® applicator.

K. Route of Administration

Subcutaneous

L. Species/Class

Growing beef steers and heifers fed in confinement for slaughter

M. Indication

For increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

N. Effect of Supplement

This supplement provides for approval of the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

II. EFFECTIVENESS

FDA concluded that SYNOVEX® ONE Grower was effective for the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter. The effectiveness of SYNOVEX® ONE Grower was demonstrated in one well-controlled, multi-site, randomized, negative control field study. The effectiveness of SYNOVEX® ONE Grower for weight gain in 400 heifers and 400 steers was compared to a negative control group of 400 heifers and 400 steers. There was no significant treatment effect on the rate of animals removed from the study, and the adverse reactions observed (primarily pneumonia, ruminal bloat, foot rot, and clinical signs of coccidiosis) were observed in both treatment groups and at a frequency typical for these common conditions encountered, treated, and managed in U.S. feedlot cattle.

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-348 dated July 31, 2014, contains dosage characterization information for the 6-pellet SYNOVEX® ONE Grass implant for use in growing beef steers and heifers on pasture (stocker, feeder, and slaughter), and the dosage characterization information for the 8-pellet SYNOVEX® ONE Feedlot implant for use in growing beef steers and heifers fed in confinement for slaughter. Both implants were approved for increased rate of weight gain for up to 200 days. The SYNOVEX® ONE Grower implant is the identical 6-pellet implant previously named SYNOVEX® ONE Grass.

B. Substantial Evidence

1. Dose Confirmation Field Study

Title: Efficacy of SYNOVEX® ONE GRASS for Increased Rate of Weight Gain in Feedlot Steers and Heifers Fed in Confinement for Slaughter (Study No. A131C-US-19-741)

Study Dates: October 29, 2019, to January 27, 2021.

Study Locations: The study was conducted in four locations in the United States: Canyon, TX (Site A), Parma, ID (Site B), Reedley, CA (Site C), and Oakland, NE (Site D). Sites were selected to represent a broad range of management and environmental conditions to provide inferential value to the U.S. beef cattle feedlot industry.

Study Design:

Objective: To evaluate the effectiveness of SYNOVEX® ONE Grass (150 mg trenbolone acetate and 21 mg estradiol benzoate) for increased rate of gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

Study Animals: A total of 800 heifers and 800 steers were enrolled across four U.S. study sites in Texas, Idaho, California, and Nebraska. Animal body weights ranged from 533 to 839 lb on the day of enrollment (Day 0), with average body weights for heifers and steers of 685 and 705 lb, respectively. Steers and heifers were acquired from livestock auctions or ranches from major cattle-producing regions of the United States. The study included healthy purebred or crossbred English or Continental breed cattle, approximately 5 to 10 months of age, and not given other implants in the 21 days prior to treatment. Cattle were excluded if they were pregnant females or intact males. Study animals were housed in outdoor pens typical of U.S. commercial feedlot design relative to pen size, pen density, and bunk space. Feed rations complied with or exceeded National Research Council Nutrient Requirements of Beef Cattle (2016). Animals had *ad libitum* access to water.

Experimental Design: This was a multi-site, randomized, negative control study, lasting approximately 200 days. The live phase of the study was from November 2019 to August 2020. The study had four sites, with two 100-head pens of steers and two 100-head pens of heifers at each site, for a total of 200 steers and 200 heifers at each site. Within each site and sex, animals of similar pre-enrollment body weight (measured on Day -2 to -1) were randomly assigned to a pen. Within a pen, animals were ordered from low to high body weight to form blocks with two animals in each block. The two animals within each block were randomly assigned to one of the two treatments (negative control or SYNOVEX® ONE Grower). Only personnel conducting treatment administration and implant evaluations had access to treatment records during the study. All other personnel involved in the conduct of the study were masked to treatment assignments until the end of the animal phase of the study. The study was conducted according to Good Clinical Practice guidelines.

Drug Administration: Animals in the SYNOVEX® ONE Grower group were given a single SYNOVEX® ONE Grower implant, containing 150 mg trenbolone acetate and 21 mg estradiol benzoate in an extended-release coating, placed subcutaneously in the middle-third of the back of the ear using the Synovex® applicator, per label instructions. Animals in the control group were sham-implanted, in which the implant needle was inserted with no delivery, using a technique identical to that of the treated group. Treatments were administered on the day of enrollment (Day 0).

Measurements and Observations: Individual body weights were collected for all animals on the day of enrollment (Day 0) and the scheduled final day of the study, which varied across sites from 200 to 204 days after implantation, according to when animals were projected to reach a marketable weight. Animals were fasted for 12 hours prior to collection of the scheduled body weights. For any animals removed from the study early due to severe illness, injury, death, or for exhibiting "buller steer" behaviors (a steer experiencing excessive mounting by other steers), body weights were obtained at the time of removal and used in the analysis. Daily feed delivery and feed removal (as needed) was collected to ensure that study animals were provided adequate nutrition.

To evaluate implant site safety, individual ear evaluations were conducted on day 35 and the final study day to detect ear abscesses or other abnormalities, and the presence of an implant. All animals were observed twice daily for any general health abnormalities. Any abnormal animals were further evaluated, and illnesses, injuries, and treatments were documented.

Animals were shipped to the slaughter facility after the final body weight measurement (from the same day up to 29 days after, depending on site and slaughter facility availability). Animals were observed for overall health and ambulatory status when loading and unloading for shipment. The planned carcass variables were not collected due to the impact of the COVID-19 pandemic on access to the slaughter facilities. To estimate the potential effects of SYNOVEX® ONE Grower on carcass characteristics, the sponsor developed a literature-based database of growth performance and carcass characteristics of implanted steers; refer to Section II.B.2 below.

Statistical Methods:

The primary effectiveness variable, average daily gain (ADG), was calculated using the following equation:

$$ADG = \frac{(Final\ animal\ weight - initial\ animal\ weight)}{Total\ number\ of\ days\ animal\ was\ on\ the\ study}$$

Five animals were excluded from analysis of ADG: four due to inappropriate enrollment of reproducing animals (pregnant female and intact males) and the death of one animal early in the study period that was determined as unrelated to treatment. Statistical analysis of ADG used a general linear mixed model with the fixed effects of treatment, sex, and treatment by sex interaction, and the random effects of site, pen within site and sex, site by

treatment interaction, site by sex interaction, and site by treatment by sex interaction. The criterion for success was a significant increase in ADG for the treated group compared to the control group using a two-sided alpha level of 0.05.

An analysis of early removal rate (due to severe illness, injury, death, or for exhibiting "buller steer" behaviors) was conducted using a generalized linear mixed model with binomial distribution and logit link and the fixed and random effects same as those described above for ADG.

Results:

Initial and final body weights for animals in the control and SYNOVEX® ONE Grower groups are shown in Table II.1. The final analysis had 796 cattle in the control group (399 heifers and 397 steers) and 799 cattle in the SYNOVEX® ONE Grower group (400 heifers and 399 steers).

Table II.1 Initial and Final Body Weights (lb) Across Sex and Site.

Treatment	Animals, Number	Initial body weight, lb	Final body weight, lb
Control	796	695.2	1278.7
SYNOVEX® ONE Grower	799	694.5	1340.8

Initial and final body weights were used to calculate ADG, as described above. There was not a significant treatment by sex interaction for ADG (*P-value* = 0.0526); therefore, steers and heifers were pooled for analysis. As shown in Table II.2, ADG (lb/d) was significantly different and greater (*P-value* = 0.0010) for the animals treated with SYNOVEX® ONE Grower compared to the control group animals (3.16 lb/d versus 2.85 lb/d, respectively) over the entire study period (200 to 204 days, depending on site).

Table II.2 Pooled Statistical Analysis of Average Daily Gain (lb/day).

Treatment	Animals, Number	Least Squares Mean (lb/day)	Standard Error	***P-value****
Control	796	2.85	0.035	0.0010
SYNOVEX® ONE Grower	799	3.16	0.035	

* Treatment comparison across sex of animals; treatment by sex interaction was not significant (*P-value* = 0.0526).

The initial body weights of heifers and steers within each site are shown in Table II.3. The initial body weights of animals varied by sex and by site, but within sex and site the initial body weights were similar between animals assigned to the control and SYNOVEX® ONE Grower groups.

Table II.3 Summary of Initial Body Weight (lb) by Sex and Site.

Sex	Treatment	Site A	Site B	Site C	Site D
Heifers	**Control**	641.3	670.0	675.2	752.4
Heifers	**SYNOVEX® ONE Grower**	643.8	669.3	678.1	751.5
Steers	**Control**	668.1	717.5	716.3	721.0
Steers	**SYNOVEX® ONE Grower**	667.3	714.4	711.4	720.1

The final body weights of heifers and steers within each site are shown in Table II.4. The effect of SYNOVEX® ONE Grower on increased weight gain over 200 days can be observed across both sexes and all four study sites.

Table II.4 Summary of Final Body Weight (lb) by Sex and Site.

Sex	Treatment	Site A	Site B	Site C	Site D
Heifers	**Control**	1190.7	1247.6	1217.0	1302.1
Heifers	**SYNOVEX® ONE Grower**	1241.7	1305.3	1264.6	1339.3
Steers	**Control**	1293.1	1313.8	1329.1	1334.0
Steers	**SYNOVEX® ONE Grower**	1349.8	1397.3	1418.8	1404.0

This study demonstrates that SYNOVEX® ONE Grower (trenbolone acetate and estradiol benzoate extended-release implants) is effective for the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

Adverse Reactions:

Adverse reactions at the implant site were uncommon. These reactions were observed in approximately 2.0% of animals on these studies; of the 800 animals enrolled in the SYNOVEX® ONE Grower group, 16 had implant reactions at 35 days after implantation and 14 animals (7 previously noted and 7 new animals) had implant reactions at 200 days after implantation. The implantation site reactions were mild, such as swelling, fluid, or abscess.

Abnormal health events occurred for common conditions in beef cattle fed in confinement for slaughter. Over all 1,600 animals enrolled in the 200-day study, 120 animals with abnormal health events were reported (control, n=51; SYNOVEX® ONE Grower, n=69), see Table II.5. Abnormal health events were observed in both treatment groups. The most common abnormal health events were pneumonia or pleuritis, ruminal bloat, and foot rot and clinical signs of coccidiosis that occurred at a single site.

Table II.5 Summary of abnormal health events.

Category	Abnormal Health Event	Control	SYNOVEX® ONE Grower	Total
Respiratory	Pneumonia	18	29	47
Respiratory	Pleuritis	1	1	2
Digestive	Ruminal Bloat	7	14	21
Digestive	Coccidiosis	6	6	12
Skin/Appendage	Foot rot	4	9	13
Musculoskeletal	Lameness, laminitis, or arthritis	4	3	7
Injury	Fracture, lameness or edema from injury, or laceration	4	3	7
Eye	Pinkeye	1	1	2
Cardiovascular	Disorder or failure	0	2	2
Systemic	Depression or loss of condition	2	0	2
Systemic	Clostridial infection	1	0	1
Renal/Urinary	Urinary calculi	0	1	1
Reproductive	Ovarian tumor	1	0	1
Reproductive	Dystocia*	1	0	1
Behavioral	Buller	1	0	1
	Total	**51**	**69**	**120**

* Occurred in an inappropriately enrolled reproducing (pregnant) female

Abnormal health events generally resolved. Some enrolled animals were removed from the study early due to severe illness, injury, death, or for exhibiting "buller steer" behaviors. Only one steer (control group) was removed for exhibiting "buller steer" behaviors. There was no significant effect of SYNOVEX® ONE Grower on the early removal rate compared to the control group. Because there was not a significant treatment by sex interaction, steers and heifers were pooled for analysis. The early removal rate did not differ for animals treated with SYNOVEX® ONE Grower compared with control group animals (3.06% versus 2.35%, respectively; see Table II.6). Re-analysis of this variable excluding the four inappropriately enrolled animals did not change the conclusion.

Table II.6 Analysis of early removal of enrolled animals.

Treatment	Number Enrolled	Number Removed	Removal Rate (%)
Control	800	19	2.35
SYNOVEX® ONE Grower	800	27	3.06

The abnormal health events (primarily pneumonia, ruminal bloat, foot rot, and clinical signs of coccidiosis) were observed in both treatment groups and at a frequency typical for these common conditions encountered, treated, and managed in U.S. feedlot cattle. There was no effect of treatment on the rate of animals removed from the study. The study supports the safe use of SYNOVEX® ONE Grower for the proposed conditions of use on the labeling.

Conclusions: This study demonstrates that SYNOVEX® ONE Grower (trenbolone acetate and estradiol benzoate extended-release implants) is safe and effective for the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

2. Carcass Characteristics Literature Database and Modeling

   The sponsor developed a literature-based database of growth performance and carcass characteristics of implanted steers (27 sources; 10,400 animals) and heifers (10 sources; 4,457 heifers). Models were developed to use the measured live growth performance of growing beef steers and heifers fed in confinement for slaughter to estimate the potential effects of SYNOVEX® ONE Grower on carcass characteristics. Based upon the observed effects of SYNOVEX® ONE Grower on ADG as shown in Table II.2 above, the models to estimate the effects of SYNOVEX® ONE Grower on carcass characteristics of growing beef steers and heifers predicted that treatment effects would be similar to those previously reported for the higher-dose SYNOVEX® ONE Feedlot, as summarized in the original approval of NADA 141-348 dated July 31, 2014. Thus, the product labeling contains a statement, "NOTE: The administration of SYNOVEX® ONE Grower may result in decreased marbling scores when compared to non-implanted steers and heifers."

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-043 dated February 22, 1996, contains a summary of target animal safety studies for growing beef steers fed in confinement for slaughter. The FOI Summary for the supplemental approval of NADA 141-043 dated September 30, 1998, contains a summary of target animal safety studies for growing beef heifers fed in confinement for slaughter.

As summarized in the original approval of NADA 141-348 dated July 31, 2014, these studies supported the safety for the approval of both the higher dose 8-pellet SYNOVEX® ONE Feedlot and the lower dose 6-pellet SYNOVEX® ONE Grass (now SYNOVEX® ONE Grower) implants. The target animal safety of SYNOVEX® ONE Grower was evaluated under intended use conditions in the dose confirmation effectiveness study (see Section II.B above). There were no animal safety concerns raised by the evaluation of animal health data in these studies. In addition, pharmacovigilance information for NADA 141-348 was evaluated for the currently approved uses of the 6-pellet SYNOVEX® ONE Grass implant in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) and the higher dose 8-pellet SYNOVEX® ONE Feedlot implant in growing beef steers and heifers fed in confinement for slaughter. Taken together, the target animal safety studies cited under NADA 141-043 and the animal health data from the effectiveness study support the current new animal drug application for use of SYNOVEX® ONE Grower for growing beef steers and heifers fed in confinement for slaughter.

To provide for safe and effective use of the product, the labeling for SYNOVEX® ONE Grower includes animal safety warnings that bulling has occasionally been reported in implanted steers and heifers, and vaginal and rectal prolapse, udder development, ventral edema and elevated tailheads have occasionally been reported in heifers administered SYNOVEX® ONE Grower implants. In addition, because safety and effectiveness have not been evaluated, labeling prohibits the use of this product:

- 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 within each separate production phase:
  – growing beef steers and heifers on pasture (stocker, feeder, and slaughter).
  – growing beef steers and heifers fed in confinement for slaughter.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

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

- SYNOVEX® ONE Grower is 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,
- SYNOVEX® ONE Grower is not used to treat gastroenteritis or other bacterial diseases in humans,
- SYNOVEX® ONE Grower (or a similar class representative) is not under development to treat a bacterial disease in humans, and
- SYNOVEX® ONE Grower is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined there was no need to provide additional microbial food safety (antimicrobial resistance) information or data regarding this approved use of SYNOVEX® ONE Grower in growing beef steers and heifers fed in confinement for slaughter.

B. Toxicology

<u>Trenbolone</u>

The Acceptable Daily Intake (ADI) for total residue of trenbolone is 0.4 µg/kg of body weight per day, as codified under 21 CFR §556.739. Reassessment of the ADI was not needed for this supplemental approval. The FOI Summaries for the original approval of NADA 141-043, dated February 22, 1996, and for the supplemental approval, dated September 30, 1998, contain a summary of all toxicology studies and information.

Based on the codified ADI of 0.4 µg/kg of body weight per day and 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 ppb for muscle, 240 ppb for liver, 480 ppb for kidney, and 480 ppb for fat.

Estradiol

Estradiol is regulated on the basis of allowable incremental increases for residues. Based on the old food consumption values, residues of estradiol or any of the related esters were not permitted in excess of the following increments above the concentrations of estradiol naturally present in untreated cattle: in uncooked edible tissues of heifers, steers, and calves: (1) 0.12 parts per billion (ppb) for muscle; (2) 0.24 ppb for liver; (3) 0.36 ppb for kidney; and (4) 0.4 ppb for fat. Using the revised food consumption values (300 g for muscle, 100 g for liver, 50 g for kidney, and 50 g for fat), the updated allowable incremental increase limits residues of estradiol in edible tissues of heifers, steers, and calves to 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 residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-348 dated July 31, 2014, contains a summary of residue chemistry studies for cattle.

This supplement does not result in any change to the previously established withdrawal period. The withdrawal period remains zero days. Refer to the FOI Summary, dated July 31, 2014.

D. Analytical Method for Residues

An official analytical method is not required for either trenbolone or estradiol residues in cattle.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SYNOVEX® ONE Grower:

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 and 21 CFR part 514. The data demonstrate that SYNOVEX® ONE Grower, when used according to the label, is safe and effective for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter. Additionally, data demonstrate that residues in food products derived from species treated with SYNOVEX® ONE Grower will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product can be marketed over-the-counter (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® ONE Grower qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental application included an effectiveness study. This exclusivity begins as of the date of our approval letter and only applies for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information

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