Date of Approval: May 20, 2026

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-348

SYNOVEX® ONE GROWER

(trenbolone acetate and estradiol benzoate extended-release implants)

growing beef steers and heifers in a dry lot

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 in a dry lot.

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 in a dry lot. 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), and 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). It was initially marketed as SYNOVEX® ONE Grass but was renamed SYNOVEX® ONE GROWER. SYNOVEX® ONE GROWER is for use in growing beef steers and heifers on pasture, in feedlots, and now also in a dry lot.

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.

Target Animal Safety and Effectiveness

FDA did not require the sponsor to conduct new effectiveness studies for this supplemental approval. Effectiveness was supported by the following:

- The multi-site field effectiveness studies previously conducted by the sponsor to show that SYNOVEX® ONE GROWER increases average daily weight gain (ADG) for up to 200 days in pasture beef cattle and feedlot beef cattle.

- A literature-based argument comparing the physiology, management, housing, and nutrition of dry lot cattle to pasture beef cattle and feedlot beef cattle.

- Characterization of the ADG response across beef cattle subclasses (dry lot, pasture, and feedlot) given the same implant using data from studies conducted for previous approvals of SYNOVEX Choice® (NADA 141-043), which is a lower-dose implant of trenbolone acetate and estradiol benzoate.

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 uses of SYNOVEX® ONE GROWER (NADA 141-348) in growing beef steers and heifers on pasture and in growing beef steers and heifers fed in confinement for slaughter.

- Target animal safety information evaluated in the field effectiveness studies previously conducted by the sponsor for SYNOVEX® ONE GROWER in pasture beef cattle and feedlot beef cattle. The studies did not raise any animal safety concerns.

- The similar physiology of growing beef steers and heifers in a dry lot to pasture beef cattle and feedlot beef cattle.

Taken together, this information supports the target animal safety of SYNOVEX® ONE GROWER in growing beef steers and heifers in a dry lot.

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, one implantation in the dry lot stage, and one implantation in the feedlot stage. Therefore, the labeling for SYNOVEX® ONE GROWER prohibits more than one implantation during each stage of growth (pasture, dry lot, 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, because the drug is not an antimicrobial, FDA determined that the sponsor did not need to provide information regarding microbial food safety for this supplemental approval.

FDA determined that it was not necessary to reassess the acceptable daily intake (ADI) and safe concentrations for total residue of trenbolone for this supplemental approval. 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 information 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 six 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 in a dry lot

M. Indication

For increased rate of weight gain for up to 200 days in growing beef steers and heifers in a dry lot.

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 in a dry lot.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The FOI Summary for the original approval of NADA 141-348 dated July 31, 2014, contains dosage characterization information for the use of this dosage in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) to increase rate of weight gain for up to 200 days.

B. Substantial Evidence

The Food and Drug Administration (FDA) did not require effectiveness studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-348 dated July 31, 2014, and supplemental approval dated October 29, 2021, contain information for establishing substantial evidence of effectiveness for SYNOVEX® ONE GROWER for increased rate of weight gain for up to 200 days in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) and in growing beef steers and heifers fed in confinement for slaughter, respectively. A literature-based argument was submitted to compare the physiology, management, housing, and nutrition of growing beef steers and heifers in a dry lot to the animal subclasses for which the response to SYNOVEX® ONE GROWER had been previously evaluated: growing beef steers and heifers on pasture (stocker, feeder, and slaughter) and growing beef steers and heifers fed in confinement for slaughter.

To further support this comparison, information used for previous original and supplemental approvals of a different implant, SYNOVEX Choice® (NADA 141-043), was provided. The SYNOVEX Choice® implant contains four uncoated pellets, each pellet containing 25 mg trenbolone acetate and 3.5 mg estradiol benzoate, to provide a total of 100 mg of trenbolone acetate and 14 mg of estradiol benzoate. The SYNOVEX® ONE GROWER implant contains six of the same pellets but coated for extended release. The SYNOVEX Choice® studies were used to establish the relationship of ADG response to an identical implant for increased rate of weight gain across all three animal subclasses. The FOI Summary for the supplemental approval of NADA 141-043 dated December 19, 2024, contains information for substantial evidence of effectiveness for SYNOVEX Choice® in growing beef steers and heifers on pasture (stocker, feeder, and slaughter). The FOI Summary for the supplemental approval of NADA 141-043 dated April 5, 2024, contains information for substantial

evidence of effectiveness for SYNOVEX Choice® in growing beef steers and heifers in a dry lot. The FOI Summaries for the supplemental approval of NADA 141-043 dated October 3, 2002, and supplemental approval of NADA 141-043 dated August 3, 2014, contain information for substantial evidence of effectiveness for SYNOVEX Choice® in growing beef steers and heifers fed in confinement for slaughter. These data were used to support the expected responses of the animal subclass given the same implant and under the management conditions of use appropriate for the animal subclass.

The characterization of the animal subclass and response to treatment using the provided literature and study information for SYNOVEX Choice® supports the extension of findings of substantial evidence of effectiveness for SYNOVEX® ONE GROWER for increased rate of weight gain for up to 200 days in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) and in confinement for slaughter to support the substantial evidence of effectiveness of SYNOVEX® ONE GROWER for increased rate of weight gain for up to 200 days in growing beef steers and heifers in a dry lot.

III. TARGET ANIMAL SAFETY

FDA did not require target animal safety studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-348 dated July 31, 2014, and supplemental approval dated October 29, 2021, relied on information used for previous original and supplemental approvals of NADA 141-043 for SYNOVEX PLUS®. The SYNOVEX PLUS® implant contains eight uncoated pellets, each pellet containing 25 mg trenbolone acetate and 3.5 mg estradiol benzoate, to provide a total of 200 mg of trenbolone acetate and 28 mg of estradiol benzoate. The SYNOVEX® ONE GROWER implant contains six of the same pellets (to provide a total of 150 mg of trenbolone acetate and 21 mg of estradiol benzoate) with an additional porous polymer film coating that extends the pay-out period.

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 groups 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® ONE GROWER in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) was evaluated under intended conditions of use in a multi-location field study, as described in the FOI Summary for the original approval of NADA 141-348 dated July 31, 2014. The safety of SYNOVEX® ONE GROWER in growing beef steers and heifers fed in confinement for slaughter was evaluated under intended conditions of use in a multi-location field study, as described in the FOI Summary for the supplemental approval of NADA 141-348 dated October 29, 2021. There were no animal safety concerns raised by the evaluation of animal health data in these effectiveness studies. In addition, pharmacovigilance information for NADA 141-348 was evaluated for the currently approved uses of the 6-pellet SYNOVEX® ONE GROWER implant in growing beef steers and heifers on pasture (stocker, feeder, and slaughter) and in growing beef steers and heifers fed in confinement for slaughter. The animals in these studies are

physiologically representative of growing beef steers and heifers in a dry lot, such that the findings of these studies and pharmacovigilance information are pertinent to this approval. Taken together, the target animal safety studies cited under NADA 141-043, the animal health data from the previous effectiveness studies for SYNOVEX® ONE GROWER, and the pharmacovigilance information support the current new animal drug application for use of SYNOVEX® ONE GROWER for growing beef steers and heifers in a dry lot.

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 that vaginal and rectal prolapse, udder development, ventral edema and elevated tailheads have occasionally been reported in heifers administered these implants.

Labeling prohibits the use of SYNOVEX® ONE GROWER as follows:

- Not approved 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 in a dry lot;
  - growing beef steers and heifers fed in confinement for slaughter.

  Safety and effectiveness following reimplantation have not been evaluated.
- Do not use in beef calves less than 2 months of age, dairy calves, and veal calves because effectiveness and safety have not been established.
- Do not use in animals intended for subsequent breeding, or in dairy cows.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

This drug is not an antimicrobial. Therefore, the Agency determined that a microbial food safety assessment was not required for this supplemental approval.

B. Toxicology

Trenbolone

Reassessment of the ADI was not needed for this supplemental approval. The codified ADI for total residue of trenbolone is 0.4 µg/kg of body weight per day, as listed under 21 CFR 556.739. The safe concentrations for total residues of trenbolone in individual edible tissues of cattle are: 80 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 allowable incremental increases. Residues of estradiol are not permitted in excess of the following codified 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 (21 CFR 556.240).

C. Residue Chemistry

FDA 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 changes to the previously established withdrawal period. The withdrawal period remains zero days. Refer to the FOI Summary for NADA 141-348, 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:

USER SAFETY WARNINGS: 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® ONE GROWER, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above. Additionally, data demonstrate that residues in food products derived from cattle 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 effectiveness information. This exclusivity begins as of the date of our approval letter and only

applies to the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers in a dry lot.

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.