Date of Approval: February 13, 2017

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-445

Revalor®-XR

Trenbolone acetate and estradiol extended-release implant

Extended- and delayed-release implant

Beef steers and heifers fed in confinement for slaughter

For increased rate of weight gain and improved feed efficiency during 70 to 200 days after implantation in beef steers and heifers fed in confinement for slaughter.

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-445

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

Revalor®-XR

D. Established Name

Trenbolone acetate and estradiol extended-release implant

Note: The product's dosage form exhibits both extended- and delayed-release properties, and these properties are further characterized in the "Description" and "Indications for Use" sections of product labeling. However, per United States Pharmacopeia (USP) nomenclature guidelines, drug products exhibiting both extended- and delayed-release characteristics are referred to as "extended-release" in their product established name.

E. Pharmacological Category

Steroid hormone

F. Dosage Form

Extended- and delayed-release implant

G. Amount of Active Ingredient

One dose (implant) contains 200 mg of trenbolone acetate and 20 mg estradiol in 10 coated pellets, each containing 20 mg trenbolone acetate and 2 mg estradiol.

H. How Supplied

Ten doses (implants) are provided in a cartridge and each box contains 10 cartridges (100 implants)

I. Dispensing Status

OTC

J. Dosage Regimen

One dose (implant) containing 200 mg trenbolone acetate and 20 mg estradiol is administered to each animal. The implant is placed under the skin on the posterior aspect of the ear by means of an implanting tool.

K. Route of Administration

Subcutaneous implantation on the posterior aspect of the ear by means of an implanting tool. The implanting tool is available from Intervet, Inc.

L. Species/Class

Beef steers and heifers fed in confinement for slaughter

M. Indication

For increased rate of weight gain and improved feed efficiency during 70 to 200 days after implantation in beef steers and heifers fed in confinement for slaughter.

NOTE:
During the investigational stages, Revalor®-XR was identified as Revalor®-200 C.

II. EFFECTIVENESS

A. Dosage Characterization

Two multi-site dose titration and field effectiveness studies, one in beef steers and one in beef heifers, were conducted for the approval of Revalor®-200 (NADA 140-992) and were previously accepted by the Agency as evidence of the effectiveness of this dose (200 mg trenbolone acetate and 20 mg estradiol) for increased rate of weight gain and improved feed efficiency for beef steers and heifers fed in confinement for slaughter.

1. Field Effectiveness Studies in Beef Steers Fed in Confinement for Slaughter:

   The effectiveness studies summarized in the Freedom of Information (FOI) Summary for NADA 140-992 (approved November 29, 1999) in steers support the dose of trenbolone acetate and estradiol in the extended-release (10 polymer coated pellets) components of Revalor®-XR.

2. Field Effectiveness Studies in Beef Heifers Fed in Confinement for Slaughter:

   The effectiveness studies summarized in the FOI Summary for NADA 140-992 (approved December 6, 2001) in heifers support the dose of trenbolone acetate and estradiol in the extended-release (10 polymer coated pellets) components of Revalor®-XR.

B. Substantial Evidence

1. Type of Study: Multi-center field effectiveness study

   a. Title: "Multi-center field dose confirmation study for clinical efficacy and safety of a long acting trenbolone acetate and estradiol extended release implant (Revalor®-200 C) on the performance and carcass characteristics of feedlot heifers and steers."

   b. Locations: The study was conducted at four feedlots, one each in California, Texas, Idaho, and Nebraska. Site selection covered a broad

range of management and environmental conditions representative of the U.S. feedlot industry. Site identifier and locations are listed in Table II.1.

Table II.1. Site identifier and study locations

Site	Location
A	Tulare, CA
B	Canyon, TX
C	Parma, ID
D	Oakland, NE

c. Study Design:

1) Objective: To demonstrate that Revalor®-XR increases average daily gain (ADG) and improves feed efficiency (FE) during 70 to 200 days after implantation in beef steers and heifers fed in confinement for slaughter.
2) Study Animals: A total of 720 steers and 720 heifers weighing on average 614 and 592 pounds, respectively, were enrolled in the study. In each of four sites, 160 or 200 steers and 160 or 200 heifers were enrolled and randomly assigned to one of two treatment groups (n = 80 or 100 per gender group; 8 or 10 per pen).
3) Experimental design: The study utilized a randomized complete block design. Animals were blocked on the basis of sex and weight, and randomly assigned to one of two treatment groups.
4) Treatment Groups: There were two treatment groups: Control (sham) and Revalor®-XR.
5) Drug Administration: Implants were placed subcutaneously in the middle third of the back of the ear in treated animals. Control animals were sham implanted (implant needle inserted in ear but no implant was inserted) using a technique identical to that of the implanted cattle. Personnel who collected study data (other than data related to test article administration and accountability) were masked to treatments.
6) Measurements and Observations: Individual body weights were collected for all animals on Day 0, 70, and 140 after implantation and just prior to shipment for slaughter for calculation of ADG. Feed consumption (feed issued minus feed weighback) was recorded to allow calculation of FE. All animals within a study site were weighed when most of the cattle at a site were judged to have reached market condition (Day 194 to 227 for steers; Day 170 to 219 for heifers) and then transported for slaughter. Carcass data (calculated yield grade, quality grade, marbling score, hot carcass weight, ribeye area, maturity score, and the incidence of liver abscesses) were collected at slaughter.

   To evaluate implant safety, individual ear evaluations to detect ear abscesses, other ear abnormalities, and the presence of an implant were performed for all cattle at Day 35 and 70. In addition, all animals were observed daily during the study for abnormalities. Illnesses, injuries, and treatments were documented and evaluated.

d. Statistical Methods: The effectiveness variables, ADG and FE from day 0 to final measurement, and the carcass variables (calculated yield grade, quality grade, marbling score, hot carcass weight, ribeye area, maturity score, and dressing percentage), were analyzed by linear mixed model analysis. Treatment was a fixed effect in the model. Study site, study site by treatment interaction, and blocks nested within site were random effects. Liver abscesses were evaluated using a generalized linear mixed model (the GLIMMIX procedure in SAS), with an assumed binomial distribution and logit link. The proportion of cattle in each pen with an ear abscess was determined and then subjected to an angular transformation (arcsine square root).

e. Results: Both ADG (P=0.0006) and FE (P=0.0010) were significantly improved in the Revalor®-XR group versus the negative control group for the overall (Day 0 to final) study period (Table II.2). The treatment by sex interaction was not statistically significant (P>0.35) for either variable.

Table II.2. Analysis of ADG and FE during the overall study

Variable	Control	Revalor®-XR	MS Error	P-value
ADG day 0 to final	2.757	3.111*	0.0400	0.0006
FE day 0 to final	6.720	6.115*	0.5439	0.0010

‡ADG = lb per head per day; FE = lb feed per lb of body weight gain
* Versus control, P <0.05

ADG and FE for Day 0 to Day 70 were similar for the Revalor®-XR group versus the control group (Table II.3).

Table II.3. Analysis of ADG and FE during Day 0 to Day 70 of the study

Variable	Control	Revalor®-XR	Improvement Versus Control
ADG day 0 to day 70	3.05	3.05	0.0%
FE day 0 to day 70	6.16	6.07	1.5%

‡ADG = lb per head per day; FE = lb feed per lb of body weight gain

The main effect of treatment was statistically significant for hot carcass weight (P<0.0001) and ribeye area (P=0.0004) (Table II.4). The treatment by sex interaction was not statistically significant (P>0.14) for any of the variables.

Table II.4. Analysis of carcass data

Variable	Control	Revalor®-XR	MS Error	P-value
Calculated Yield Grade	3.0333	3.0001	0.07154	0.7124
Quality Grade Number‡	775.69	762.17	530.15	0.3387
Marbling Score Number‡‡	48.7222	46.8856	9.2018	0.3431
Hot Carcass Weight, lb/head	702.89	750.58*	398.86	<0.0001
Ribeye Area, sq. inches	12.4133	13.2518*	0.1862	0.0004
Maturity Score	51.6843	54.6405	20.24	0.1175
Dressing Percentage (%)	59.9624	60.3139	0.4727	0.1965
Liver Abscess Percentage (%)	28.79	29.34	------	0.9557

‡ Quality grade prime = ≥900, choice = 700-899 and select = 600-699
‡‡ Marbling score of 30 to 39 = Select, 40 to 69 = Choice, 70+ = Prime
* Versus control, P < 0.05

f. Adverse Reactions: No adverse reactions attributable to the drug were reported in this study. Animal removals and adverse events were for common feedlot ailments and the frequency of occurrence was not related to use of the drug. No bulling or other undesirable behaviors were observed in any of the study cattle. For ear abscesses, the main effect of treatment was not statistically significant (P>0.15) on either evaluation day. The treatment by sex interaction was also not statistically significant (P>0.32) for this outcome on either study day. The incidence of abscesses (back transformed data) was 0.06% and 0.00% in the Revalor®-XR group compared to the control group (0.00%) on Days 35 and 70, respectively. Across the four study sites, the percentage of missing implants or pellets was 3.5% and 3.8% on Days 35 and Day 70, respectively.

A total of 177 summarized abnormal daily observations (primarily bovine respiratory disease) were reported, 96 in the control group and 81 in the Revalor®-XR group. Fifteen heifers and 23 steers died or were removed from the study (21 control and 17 Revalor®-XR; Table II.5). No trend in abnormal daily observations, cattle deaths, or removals by treatment group was observed.

Table II.5. Animal removal by treatment and study site

Site	Control	Revalor®-XR
A	0	2
B	6	5
C	10	7
D	5	3
TOTAL	**21**	**17**

g. Conclusions: This study demonstrated that Revalor®-XR is safe and effective for increased rate of weight gain and improved feed efficiency during 70 to 200 days after implantation in beef steers and heifers fed in confinement for slaughter. These results also show the magnitude of trenbolone acetate and estradiol released from this delayed- and extended-release delivery system resulted in measurable increases in the rate of weight gain and feed efficiency during 70 to 200 days after

implantation of beef steers and heifers fed in confinement for slaughter, due to the delayed- and extended-release characteristics of this implant (see Section II.B.2. Implant Payout Study). Incidence of abnormal health events and deaths was no higher in the implanted cattle versus the control cattle. Ear abnormalities in the Revalor®-XR treated cattle (abscesses, missing implants) were minimal.

2. Type of Study: Implant Payout Study

   a. Title: "Evaluation of implant payout of trenbolone and estradiol following implantation of steers and heifers with a modified release Revalor®-200 C formulation"

   b. In-Life Testing Facility: Merck Animal Health, Terre Haute, IN

      Analytical Laboratory: Catalent Pharma Solutions, Morrisville, NC

   c. Study Design:

      1) Objective: To evaluate the implant payout profiles of trenbolone acetate (TBA) and estradiol (E2β) in this implant formulation over a 210 day period in beef steers and heifers following implantation (Day 0).
      2) Study Animals: Beef steers and heifers were included in this study (five animals per gender per explant day). The animals were distributed to pens by sex and allowed access to feed and water. The cattle underwent acclimation in the study for a period of at least 14 days prior to dosing. The animals were kept in outdoor pens by sex. Daily environmental conditions (current, high and low temperatures, and humidity, and the amount and type of precipitation) for the location of the testing facility were reported.
      3) Experimental design: The study utilized a randomized complete block design. Animals were blocked on the basis of sex, and randomly assigned to one of seven treatment groups.
      4) Treatment Groups: There were seven different explant day treatment groups: Day 0, 35, 70, 105, 140, 175, or 210.
      5) Drug Administration: The test article was administered in the left ear of all animals. Prior to implanting, the posterior aspect of the ear to be implanted was clipped to remove hair. The ear was then cleaned of hair clippings and other extraneous material and dried prior to implanting. An individual experienced in implanting cattle administered the test article. The implant was placed subcutaneously in the middle of the posterior aspect of the ear with care to avoid implanting in or through blood vessels. All animals were dosed correctly, with no loss of pellets observed at the time of dosing.
      6) Measurements and Observations: Implants were explanted from the animals on their specified explant day (Day 0, 35, 70, 105, 140, 175, or 210). Explants were removed from each animal according to the following procedure: each animal was first euthanized and then the whole ear was immediately removed by a sharp knife. Each ear was placed in a sealed container (labeled by animal ID) and transported to the on-site laboratory for dissection and careful removal of all detectable implant pellets (or remnants) that could be visibly located. A magnifying glass was used as needed to identify any small (i.e.,

partially dissolved or broken) pellets. The explants were placed in sealed containers after removal and stored frozen (≤ -10°C) until transfer to the analytical laboratory. The explants were shipped frozen on dry ice to the analytical laboratory. All recovered pellets of each explant specimen were solubilized for assay. Assays were performed using a validated HPLC analysis. Lack of interference by animal tissues was confirmed prior to explant analysis.

d. Statistical Methods: Summary statistics (n, mean, standard deviation) for the assayed amount of each active ingredient were calculated at each time point. The percent of each active ingredient remaining in the implants for each animal at each explant time point was calculated. The baseline amount of each active ingredient was the amount of 200 mg TBA and 20 mg E2β present in the implant shortly after implantation (i.e., Day 0) in the animal. These percentages allowed calculation of the cumulative amount of the active ingredient released on or before the observation time.

   For TBA and E2β, the change in mean active ingredient amount at the end of each explant period was evaluated as a function of time using the Proc GLM procedure (SAS v 9.3). Comparisons of the implant content across paired sampling times was generated via a t-test using the Pdiff statement. Each of the two active ingredients (TBA and E2β) was separately tabulated. The results from all heifers and steers were combined to provide an unbiased overall estimate for each explant day.

e. Results: The active ingredients recovered from the Day 0 explants were close to the labeling indication for all samples except four explants for which the TBA was only approximately 88% in four of the five females. Recovery of both active ingredients from explants at Day 35 averaged approximately 90% of the labeling indication and the recovery generally decreased with time, except the amounts of both active ingredients on Day 140 averaged higher than Day 105.

The rate of decline in E2β and TBA implant content over time is provided in Figures 1 and 2 below.

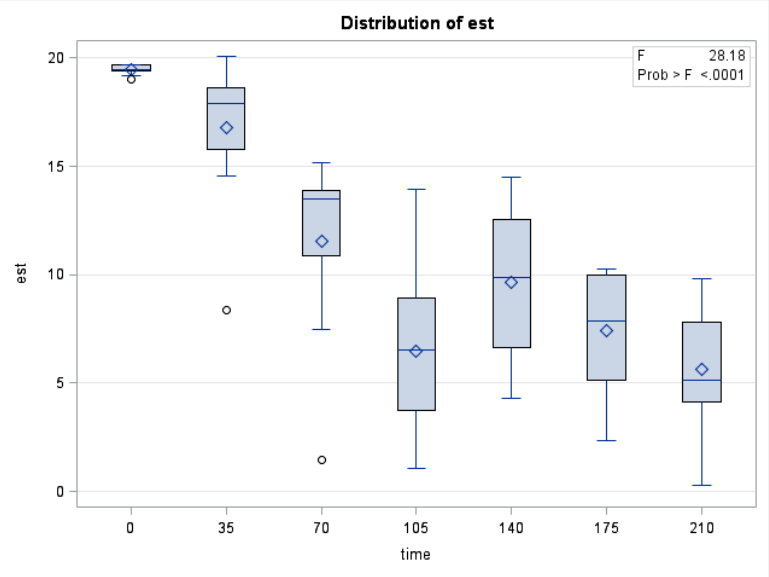

Figure 1: Relationship between E2β (est) content (Y-axis in mg) versus explant day (X axis).

Each column reflects the mean (diamond), median (line within the column), and the upper and lower quartiles (25% of the data are higher or lower than these values). The upper and lower whisker represents the upper and lower values falling within the normal distribution. Any points outside the whiskers represent data outliers. While the values remain close to 20 mg between days 0 and 35, the mg per implant rapidly decreases down to about 6.5 mg on day 105. On subsequent days, mean quantified implant content fluctuates between about 9.6 (explant day=140) to 5.64 mg (explant day=210). The upper whisker values go from about 14 mg on day 105 to 10 mg on day 210. Lower whisker values go from about 2 mg on day 105 to 0.03 mg on day 210.

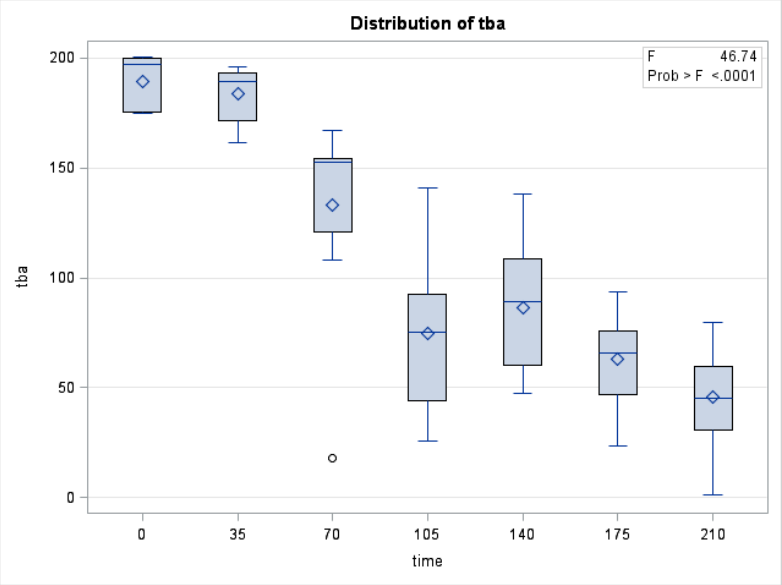

Figure 2: Relationship between TBA content (Y-axis in mg) versus explant day (X axis).

Each column reflects the mean (diamond), median (line within the column), and the upper and lower quartiles (25% of the data are higher or lower than these values). The upper and lower whisker represents the upper and lower values falling within the normal distribution. Any points outside the whiskers represent data outliers. While the values remain close to 200 mg between days 0 and 35, the mg per implant rapidly decreases down to about 75 mg on day 105. On subsequent days, mean quantified implant content fluctuates between about 86 (explant day=140) to 46 mg (explant day=210). The upper whisker values go from about 140 mg on day 105 to 80 mg on day 210. Lower whisker values go from about 25 mg on day 105 to 1.25 mg on day 210. The *in vivo* release of TBA from the implant was slightly greater than that observed for E2β.

The release of both active ingredients from the implants exhibits marked intersubject variability across all study days except days 0 and 35. No identifiable differences in product performance were observed across genders.

f. Adverse Reactions: No adverse reactions were reported in this study.

g. Conclusions: The explant data suggest that the product exhibits both delayed- and extended-release characteristics, specifically the following *in vivo* release characteristics for both TBA and E2β: Revalor®-XR exhibits a delay in E2β and TBA release for the first 35 days after implantation. The majority of drug release (approximately 57 - 65%) of the total drug release occurs from days 35 to 105. The subsequent 15% (TBA) or 5% (E2β) of the remaining drug release occurs from day 105 to 210. Due to the slightly greater release rate of TBA vs E2β, there is a small shifting in the TBA/E2β ratio during the terminal portion of the implant period. There is no difference in the *in vivo* product release characteristics as a function of gender.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this original approval. The new animal drug application for Revalor®-XR (trenbolone acetate and estradiol extended-release implant) references the target animal safety studies summarized in the FOI Summaries for NADAs 138-612, 140-992, and 140-897. The data from the field effectiveness study reported in this FOI Summary, in conjunction with the previously reported target animal safety study data for NADAs 138-612, 140-992, and 140-897, demonstrate the safety of the new animal drug for the indication and dosage regimen as described in the "General Information" section.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

The Agency evaluated the need to address the impact of the use of trenbolone acetate and estradiol on microbial food safety (antimicrobial resistance) among bacteria of public health concern in or on treated cattle. We considered that:

- Trenbolone acetate and estradiol are not normally considered to have properties that would exert antimicrobial resistance pressure towards the emergence or selection of bacteria of public health concern;
- Trenbolone acetate and estradiol are not used to treat zoonotic gastroenteritis or other diseases in humans;
- Trenbolone acetate and estradiol (or a similar compound) are not under development to treat diseases in humans; and
- Trenbolone acetate and estradiol are not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined there was no need to develop or submit for review any microbial food safety (antimicrobial resistance) information regarding this proposed use of trenbolone acetate and estradiol in cattle.

B. Impact of Residues on Human Intestinal Flora

Residues and metabolites of trenbolone acetate and estradiol are not known to have antimicrobial properties. Additionally, residues and metabolites of trenbolone acetate and estradiol have not been shown to impact bacterial populations. Therefore, at this time, the Agency does not think that residues and metabolites of trenbolone acetate and estradiol in or on edible food products from cattle treated with the compounds will impact the intestinal flora of human consumers, and there was no need to submit additional information or data to define a microbiological acceptable daily intake.

C. Toxicology

Trenbolone Acetate:

Reassessment of the toxicological acceptable daily intake (ADI) was not needed for this approval. The FOI Summary for the original approval of NADA 138-612, dated July 2, 1987, contains summaries of all toxicology studies and information.

The final ADI of trenbolone acetate (TBA) is the toxicological ADI of 0.4 µg per kg of body weight per day derived from a chronic toxicity study in female Rhesus Macaque. The ADI for trenbolone is codified under 21 CFR 556.739.

The safe concentration of total TBA residues in each edible tissue of steers and heifers is 80 ppb for muscle, 240 ppb for liver, 480 ppb for kidney, and 480 ppb for fat, based on the revised food consumption values (NADA 141-269 dated January 19, 2007).

Estradiol:

Estradiol is regulated on the basis of allowable incremental increase limits for residues. Based on the old food consumption values, residues of estradiol or any of the related esters are not permitted in excess of the following increments above the concentrations of estradiol naturally present in untreated animals: In uncooked edible tissues of heifers, steers, and calves, (1) 120 parts per trillion (ppt) for muscle; (2) 480 ppt for fat; (3) 360 ppt for kidney; and (4) 240 ppt for liver.

Using the revised food consumption values, the updated allowable incremental increase limits residues of estradiol in edible tissues of heifers, steers, and calves to 200 ppt for muscle, 600 ppt for liver, 1200 ppt for kidney, and 1200 ppt for fat.

D. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      CVM did not require total residue and metabolism studies for this approval. The FOI Summary for the original approval of NADA 138-612, dated July 2, 1987 (52 FR 24994, July 2, 1987), contains a summary of total residue and metabolism studies for trenbolone in

cattle. The highest concentration of total trenbolone residues in the edible tissues was found in the liver of cattle treated with trenbolone acetate implants. Lower concentrations of total trenbolone residues were found in the kidneys, muscle, and fat.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval. The FOI Summary for the original approval of NADA 138-612, dated July 2, 1987 (52 FR 24994, July 2, 1987), contains a summary of comparative metabolism studies for trenbolone.

c. Study to Establish Withdrawal Period

(1) Tissue Residue Depletion Study

In addition to the residue depletion study summary that follows, the NADA for Revalor®-XR references residue depletion studies summarized in the FOI Summaries for the approvals of NADAs 138-612, 140-897, 140-992, and 141-269 to demonstrate Human Food Safety. Because studies conducted for the previous approvals did not include the extended-release formulation, the following study was conducted to provide data in steers and heifers at Day 70, Day 105, and Day 154 following implantation of Revalor®-XR implant.

Study Title: "Evaluation of Tissue Residue Depletion of Trenbolone and Estradiol Following Implantation of Feedlot Steers and Heifers with a Modified Release Revalor®-200 C Formulation" - Intervet Study #S12062-00.

Objectives: To determine the concentrations of the two metabolites of trenbolone acetate (trenbolone-17α and trenbolone-17β) and 17β-estradiol in the edible tissues of steers and heifers at Day 70, Day 105, and Day 154 following implantation of Revalor®-XR.

In-Life Testing Facility: Intervet, Inc. (d/b/a Merck Animal Health), Terre Haute Research Farm, Terre Haute, IN

Analytical Testing Facility: Intervet, Inc. (d/b/a Merck Animal Health), Summit, NJ

Test Article: Revalor®-XR implant

Test Animals: 15 feedlot steers and 15 feedlot heifers weighing 242 to 330 kg at 7 days prior to implantation

Test Article Administration: For each implantation period (70 days, 105, days and 154 days), four steers (males) and four heifers (females) were implanted in the ear with one Revalor®-XR implant per animal on Day 0 of the study, with one steer and one heifer serving as untreated control animals.

Duration of Implantation: 70 days, 105 days, and 154 days

Tissue Sampling: On each of Day 70, Day 105, and Day 154 after the animals were euthanized, muscle, liver, and fat tissue samples were collected from four implanted animals and one control animal of each sex. Based on the data on file with FDA under NADAs 138-612, 140-897, 140-992, and 141-269, FDA determined that sampling liver, muscle, and fat for analyses of trenbolone and estradiol residues is adequate to ensure safety of all the edible tissues of cattle treated with Revalor®-XR.

Residue Analysis: The tissues were analyzed for 17α-trenbolone and 17β-trenbolone, and 17β-estradiol concentrations using both radioimmunoassay (RIA) methods and LC-MS/MS methods. The RIA methods were used for residue analyses for previous approvals. However, FDA concluded that in the study (Intervet Study #S12062-00), the RIA methods could not reliably quantitate the residues because key reagents (antibodies) for the methods were not of uniform quality. FDA concluded that the residue concentrations determined using the LC-MS/MS methods in the study were acceptable for residue evaluation. An approximately 1:1 ratio for 17β-trenbolone concentrations in the liver samples quantitated using the RIA method to those quantitated using the LC-MS/MS method is supported by the sponsor's data on file with FDA.

Therefore, only the residue concentrations quantitated using the LC-MS/MS methods were used for residue evaluation.

Results: The limit of detection (LOD) and lower limit of quantitation (LLOQ) for analysis of 17α-trenbolone, 17β-trenbolone, and 17β-estradiol in steers and heifer tissues by the LC-MS/MS methods are summarized in Table IV.1 and Table IV.2 below.

Table IV.1. The limit of detection (LOD) and lower limit of quantitation (LLOQ) of LC-MS/MS methods for analysis of 17α-trenbolone, 17β-trenbolone, and 17β-estradiol in steer tissues

Analyte	**Liver** LOD/LLOQ (pg/g)	**Muscle** LOD/LLOQ (pg/g)	**Fat** LOD/LLOQ (pg/g)
17α-Trenbolone	37.6/115	20.7/31.7	24.1/73.6
17β-Trenbolone	14.7/44.7	25.4/38.7	23.2/70.8
17βEstradiol	12.7/38.8	1.28/3.92	7.82/23.8

Table IV.2. The limit of detection (LOD) and lower limit of quantitation (LLOQ) of LC-MS/MS methods for analysis of 17α-trenbolone, 17β-trenbolone, and 17β-estradiol in heifer tissues

Analyte	**Liver** LOD/LLOQ (pg/g)	**Muscle** LOD/LLOQ (pg/g)	**Fat** LOD/LLOQ (pg/g)
17α-trenbolone	26.7/81.5	17.5/53.4	10.0/30.6
17β-trenbolone	18.8/57.4	17.9/54.5	11.1/33.9
17β-estradiol	14.9/45.4	3.7/11.3	8.3/25.2

The means and standard deviations (SDs) of 17α-trenbolone, 17β-trenbolone and 17β-estradiol concentrations at Day 70, Day 105, and Day 154 after implantation are summarized in Table IV.3., Table IV.4. and Table IV.5, below. Only the residue concentrations that are at or above the LLOQs are included in the calculation for the means and SDs. The SD is not calculated where only one sample had a residue value at or above the LLOQs.

Table IV.3. Mean concentration (pg/g) ± SD of 17α-trenbolone in tissues of steers and heifers at day 70, day 105, and day 154 after implantation of Revalor®-XR

Days of Implantation	Animal Number	Muscle	Liver	Fat
Day 70	4 Male	<LOQ	282.3±180.3	<LOQ
Day 70	4 Female	<LOQ	261.3±97.7	<LOQ
Day 105	4 Male	<LOQ	297.0±85.6	<LOQ
Day 105	4 Female	<LOQ	156.0±33.2	<LOQ
Day 154	4 Male	<LOQ	178.8±18.6	<LOQ
Day 154	4 Female	<LOQ	181.0±53.2	<LOQ

Table IV.4. Mean concentration (pg/g) ± SD of 17β-trenbolone in tissues of steers and heifers at day 70 and day 105 after implantation of Revalor®-XR

Days of Implantation	Animal Number	Muscle	Liver	Fat
Day 70	4 Male	48.2±3.8	307.3±104.3	226.5±167.0
Day 70	4 Female	<LOQ	94.1±46.8	91.4±58.8
Day 105	4 Male	49.0±5.7	279.8±150.6	126.4±47.2
Day 105	4 Female	55.5	120.1±59.6	84.6±27.4
Day 154	4 Male	<LOQ	101.1±29.4	90.8±12.8
Day 154	4 Female	<LOQ	197.0±64.8	149.0±49.0

Table IV.5. Mean concentration (pg/g) ± SD of 17β-estradiol in tissues of steers and heifers at day 70 and day 105 after implantation of Revalor®-XR

Days of Implantation	Animal Number	Muscle	Liver	Fat
Day 70	4 Male	6.2±1.8	<LOQ	87.2
Day 70	4 Female	<LOQ	<LOQ	52.4±28.1
Day 105	4 Male	7.7±5.2	<LOQ	52.4±27.6
Day 105	4 Female	<LOQ	<LOQ	35.8±2.3
Day 154	4 Male	5.0±0.9	<LOQ	<LOQ
Day 154	4 Female	11.4	<LOQ	26.8

Conclusions: The incurred total trenbolone residue concentrations in the liver of cattle treated with Revalor®-XR were calculated from the 17β-trenbolone concentrations reported in this study by applying a correlation of 1% for 17β-trenbolone concentration to total trenbolone residue

concentration in the liver previously applied to support the original approval of Revalor®-XS (NADA 141-269, approved January 19, 2007). The calculated concentrations of total residues of trenbolone in the liver at Day 70, Day 105, and Day 154 after the implantation were well below half of the safe concentration for total residues of trenbolone in the liver. The incremental increases of estradiol-17β concentrations in the edible tissues at Day 70, Day 105, and Day 154 after implantation were below the codified allowable incremental increases for estradiol in the respective edible tissues (21 CFR 556.240).

(2) Implant Payout Profile

The implant payout study, Intervet Study S12093-00, was summarized in the effectiveness section of this FOI Summary. Seven groups of animals with five steers and five heifers in each group were implanted with Revalor®-XR on Day 0. Implants were collected from the animals in one of the seven groups on explantation Days 0, 35, 70, 105, 140, 175, and 210 following implantation. Concentrations of trenbolone acetate and estradiol remaining in the explants were quantitated.

Conclusions: Data for trenbolone and estradiol concentrations remaining in explants at 0, 35, 70, 105, 140, 175, and 210 days after implantation demonstrated a gradual and steady payout of the steroids from the implants over the tested implantation period.

2. Target Tissue and Marker Residue

Neither a target tissue nor a marker residue assignment is needed for trenbolone acetate in cattle (see the FOI Summary for NADA 138-612, approved July 2, 1987).

A specific target tissue is not identified for residues of estradiol in cattle. Allowable incremental increases for estradiol residues are assigned for each of the edible tissues.

3. Tolerances

A tolerance for trenbolone in cattle is not needed (21 CFR 556.739; see also the FOI Summary for NADA 138-612, approved July 2, 1987).

Residues of estradiol are regulated on the basis of the codified allowable incremental increases (21 CFR 556.240).

4. Withdrawal Period

No withdrawal period is required (*i.e.*, zero-day withdrawal).

E. Analytical Method for Residues

A regulatory analytical method for monitoring trenbolone residues in cattle is not required.

A regulatory analytical method for monitoring estradiol residues in cattle is not required.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Revalor®-XR:

Not for Use in Humans. Keep this and all drugs out of the 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 Revalor®-XR, when used according to the label, is safe and effective for increased rate of weight gain and improved feed efficiency during 70 to 200 days after implantation in beef steers and heifers fed in confinement for slaughter. Additionally, data demonstrate that residues in food products derived from species treated with Revalor®-XR 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

Revalor®-XR, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the effectiveness and safety of Revalor®-XR.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.