

JUN 19 2000

**FREEDOM OF INFORMATION SUMMARY
FOR
REVALOR®-IS (TRENBOLONE ACETATE AND ESTRADIOL)**

1. GENERAL INFORMATION

NADA Number: 140-897

Sponsor: Hoechst Roussel Vet
P.O. Box 4010
Clinton, NJ 08809

Generic Names: Trenbolone Acetate and Estradiol

Trade Name: REVALOR®-IS

Marketing Status: Over the counter (OTC)

Effect of Supplement: Provides for the administration of a dose of 80 mg trenbolone acetate and 16 mg estradiol in steers fed in confinement for slaughter for increased rate of weight gain and improved feed efficiency. (Note: The sponsor currently has an approved ear implant containing 120 mg trenbolone acetate and 24 mg estradiol (Revalor®-S) - see 21 CFR 522.2477.)

2. INDICATIONS FOR USE

For increased rate of weight gain and improved feed efficiency in steers fed in confinement for slaughter.

3. DOSAGE FORM(S), ROUTE(S) OF ADMINISTRATION AND RECOMMENDED DOSAGE

Dosage Form: Implantation

Route of Administration: Subcutaneous implantation on the posterior aspect of the ear.

Recommended Dosage: One implant containing 80 mg trenbolone acetate and 16 mg estradiol. Each implant is made up of 4 pellets with each pellet containing 20 mg trenbolone acetate and 4 mg estradiol.

4. EFFECTIVENESS

This supplemental new animal drug application for Revalor®-IS references the efficacy studies summarized in the FOI for NADA 140-897 (56 FR 67175 - December 30, 1991). The data from those studies demonstrate the efficacy of the new animal drug for the indications for use

FOIS 1

and dosage as given in Sections 2 and 3 above. The summary of the efficacy (Dose Titration) studies from the 1991 FOI are also presented below.

In dose titration studies the parameters measured are the same parameters as are measured in field investigations. The dose titration studies were conducted using a uniform protocol so that the results of the studies could be pooled and summarized. The studies were conducted in the major beef producing areas of the United States.

Name and Address of Investigators:

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The purpose of the studies was to determine the dose response for trenbolone acetate (TBA) and estradiol (E2 β) ear implants on rate of weight gain and feed efficiency of confined steers. The test animals were cross-bred animals of European breeds. There were 7 to 10 animals per pen depending on study location. Each treatment was replicated 8 times (8 pens/treatments) in all three studies. The steers weighed between 700 (318 kg) and 750 (341 kg) lbs. when the studies were initiated. Eight hundred sixty-four steers were treated in these three dose titration studies.

The drug (TBA+estradiol) was given via ear implants. The implants were placed subcutaneously on the back side of the mid-ear. Each dose was made up of the appropriate number of pellets, with each pellet containing 20 mg trenbolone acetate and 4 mg estradiol. The control cattle were not implanted. The dosages given in each study were (TBA/E2 β): 0/0, 140/0, 0/30, 20/4, 80/16 and 140/28. The steers were implanted once at the initiation of the study. The termination of the studies ranged between 144 and 160 days.

Average daily gain and feed efficiency data are summarized in Table 1 for each of the three dose titration studies.

TABLE 1. SUMMARY FROM THREE DOSE TITRATION STUDIES COMPARING THE PERFORMANCE OF FEEDLOT STEERS ON VARIOUS LEVELS OF TRENBOLONE ACETATE AND ESTRADIOL

TBA/E2 β (mg/mg)	Location			
	Texas	Colorado	Nebraska	Pooled Average
Average Daily Gain (lbs)				
0/0	2.10	3.18	3.22	2.83
140/0	2.07	3.18	3.34	2.86
0/30	2.37	3.24	3.49	3.03
20/4	2.34	3.27	3.49	3.03
80/16	2.56	3.54	3.67	3.26
140/28	2.67	3.66	3.69	3.34
Feed Efficiency (lbs Dry Matter/lb Gain)				
0/0	6.44	6.24	5.89	6.19
140/0	6.52	6.09	5.73	6.11
0/30	6.04	6.28	5.69	6.00
20/4	6.21	6.15	5.61	5.99
80/16	5.79	5.97	5.39	5.72
140/28	5.57	5.79	5.44	5.60

A randomized complete block design was used for all studies and the data were pooled by analysis of variance to determine the significance of the effect of trenbolone acetate/estradiol implants on average daily gain and feed efficiency. There was a significant ($P < .05$) dose effect on both average daily gain and feed efficiency with the maximum response for both parameters plateauing at a dose of 120 mg trenbolone acetate and 24 mg estradiol. The doses of 80 to 120 mg TBA/16 to 24 mg E2 β were also shown to be significantly ($P < .05$) better than 140 mg TBA alone and 30 mg E2 β alone. A highly significant linear ($P < 0.001$) dose response was observed for both average daily gain and feed efficiency. These data indicate that TBA and E2 β are effective for the indications for use and dosage as given in Sections 2 and 3 above.

The effects of treatment on carcass parameters (yield grade, quality grade, and marbling scores) and on the incidence of liver abscesses were evaluated at slaughter. At the 140 mg TBA/28 mg E2 β dose, a 10% decrease in marbling scores was observed ($P < .05$). Because of this observed decrease in marbling scores, the following statement is required on the label for the 6 pellet dose (Revalor®-S). This statement is not required for the 4 pellet dose (Revalor®-IS). Studies have demonstrated that the administration of TBA/estradiol can

result in decreased marbling scores when compared to non-implanted steers. No effect of treatment was seen on yield grade or the incidence of liver abscesses.

5. TARGET ANIMAL SAFETY

This supplemental new animal drug application for Revalor®-IS references the target animal safety studies summarized in the FOI Summary for NADA 140-897 (56 FR 67175 - December 30, 1991). The data from those studies demonstrate the safety of the new animal drug for the indications for use and dosage as given in Sections 2 and 3 above.

6. HUMAN SAFETY

A. Toxicity Tests and Safe Concentration

The toxicity studies summarized in the FOI from NADA 138-612 (52 FR 24994 - July 2, 1987) establish the safe concentration for TBA. An acceptable daily intake (ADI) of 0.0004 mg/kg body weight/day has been established for trenbolone (64 FR 18573). Estradiol is regulated under 21 CFR 556.240 on the basis of allowable incremental increases. Residues for estradiol and related esters may not exceed the following increments above the concentrations of estradiol naturally present in the untreated animals; in the uncooked edible tissues of heifers, steers, and calves, 120 parts per trillion (ppt) for muscle, 480 ppt in fat, 360 ppt for kidney, and 240 ppt for liver.

B. Residue Depletion Study

The residue depletion study is summarized in the FOI Summary for NADA 140-897 (56 FR 67175 - December 30, 1991).

C. Withdrawal Period

As summarized in the FOI Summary for NADA 140-897 (56 FR 67175 - December 30, 1991).

D. Regulatory Method

As discussed above, no withdrawal time is required. Therefore it is not necessary to have a regulatory assay method or a confirmatory assay method for TBA or estradiol tissue residues.

7. AGENCY CONCLUSIONS

Adequate data is established to demonstrate the safe and effective use of REVALOR®-IS (ear implant containing 80 mg trenbolone acetate and 16 mg estradiol) when used in steers fed in confinement for slaughter for increased rate of weight gain and improved feed efficiency.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the use of REVALOR®-IS in steers fed in confinement for slaughter.

The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

8. LABELING

Facsimile labeling (for REVALOR®-IS) is attached as follows:

1. Cartridge Label
2. Package Insert
3. Box Label – 100 doses
4. Box Label – 1000 doses
5. Box Label – 4000 doses
6. Outer Shipping Label

000005C

Revalor[®] IS

(trenbolone acetate 80 mg and estradiol 16 mg)

**10 Implants for Steers Fed in
Confinement for Slaughter**

Distributed by: Hoechst Roussel Vet
Clinton, NJ 08809-4010

Lot Number:

Expiration Date:

WARNING

Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for Use In Humans. Implant pellets in the ear only. Any other location is in violation of Federal Law. Do not attempt salvage of implanted site for human or animal food.

STORAGE CONDITIONS:

Store in a refrigerator (2-8°C; 36-47°F) and protect from sunlight. Use before the expiration date printed on the box and on the cartridge.

PACKAGE QUANTITIES

NDC 12 799 811 01
Box of 10 x 10 cartridge implants.
Revalor®-IS Registered Trademark
Hoechst Roussel Vet

Made in France by:
Hoechst Roussel Vet

Distributed by:
Hoechst Roussel Vet
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Revalor®-IS

(trenbolone acetate and estradiol)

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

DESCRIPTION

Revalor®-IS (trenbolone acetate, CAS Registry Number 10161-34-9, and estradiol, CAS Registry Number 50-28-2) is an implant containing 80 mg trenbolone acetate and 16 mg estradiol. Each implant consists of 4 small yellow pellets. Ten implants are provided in a cartridge.

Manufactured by a non-sterilizing process.

INDICATIONS FOR USE

Increases rate of weight gain and improves feed efficiency in a slow-release delivery system.

DOSAGE:

Dosage Form:

One implant containing 80 mg trenbolone acetate and 16 mg estradiol is administered to each animal. The 4 pellets which make up the dosage of Revalor®-IS are contained in one division of the multiple dose cartridge. Ten doses are in each cartridge. The cartridge is designed to be used with a special implant gun.

Route of Administration:

The implant is placed under the skin on the posterior aspect of the ear by means of a special implanter available from Hoechst Roussel

Vet. With the animal suitably restrained, the skin on the outer surface of the ear should be cleaned. The implant is then administered by the method shown in the diagram below.

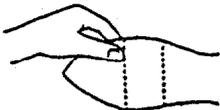


Fig. 1 - Ear of Bovine Ready for Implantation

SITE OF IMPLANTATION

After appropriately restraining the animal to allow access to the ear, cleanse the skin at the implant needle puncture site. It is subcutaneous between the skin and cartilage on the back side of the ear and below the midline of the ear. The implant must not be placed closer to the head than the edge of the cartilage ring farthest from the head. The location of insertion of the needle is a point toward the tip of the ear and at least a needle length away from the intended deposition site. Care should be taken to avoid injuring the major blood vessels or cartilage of the ear.

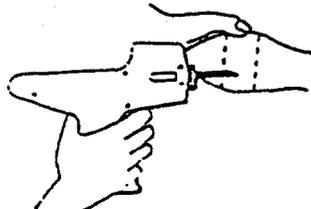
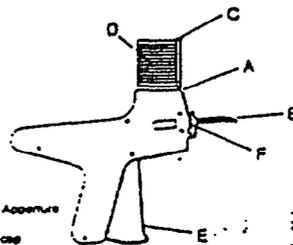


Fig. 2 - Rear View of the Bovine Ear Showing the Site for Insertion of the Implanter Needle.

METHOD OF USE

- 1. Do not remove the cap of the cartridge containing the implants.

- 2. Place the cartridge (D) (with the capped end to the front) into slot at the top of the implanter magazine (marked A on the diagram).
- 3. Gently push the cartridge into the slot until it clicks into place.
- 4. The implanter is then ready for use.
- 5. Take the ear of the animal firmly with the free hand (in the manner shown in Fig. 1). Then insert the needle into the subcutaneous tissue at the point indicated (in Fig. 2).
- 6. After inserting the needle to its full extent, squeeze the trigger (E) gradually. Allow the pellets of the implant to be deposited in a single row.
- 7. Withdraw the implanter. This will advance the cartridge one groove in the magazine and the next implant is now ready for use.
- 8. When all the implants have been administered, the cartridge will fall out of the bottom of the magazine and may be replaced by a new one.
- 9. To change the needle, loosen the needle locking nut (labeled F in Fig. 3) and replace the needle. Tighten the nut finger tight and the implanter is ready for use.



- A - Magazine Aperture
- B - Needle
- C - Cartridge cap
- D - Cartridge
- E - Trigger
- F - Needle locking nut

Fig. 3 - Diagram of the Implanter and Cartridge

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Revalor®-IS

(trenbolone acetate and estradiol)

PACKAGE QUANTITIES:

Box of 10 x 10 cartridge implants
Contains 100 doses in ten cartridges with ten implants per cartridge, each dose contains 4 small yellow pellets. Each pellet contains 20 mg of trenbolone acetate and 4 mg estradiol.

STORAGE CONDITIONS:

Store in a refrigerator (2-8°C; 36-47°F) and protect from sunlight. Use before the expiration date printed on the box and on the cartridge.

USES:

Increases rate of weight gain and improves feed efficiency in a slow-release delivery system

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

Box of 10 x 10 Cartridge Implants

Manufactured by a non-sterilizing process

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Revalor®-IS Registered trademark Hoechst Roussel Vet

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Revalor®-IS
(trenbolone acetate and estradiol)

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

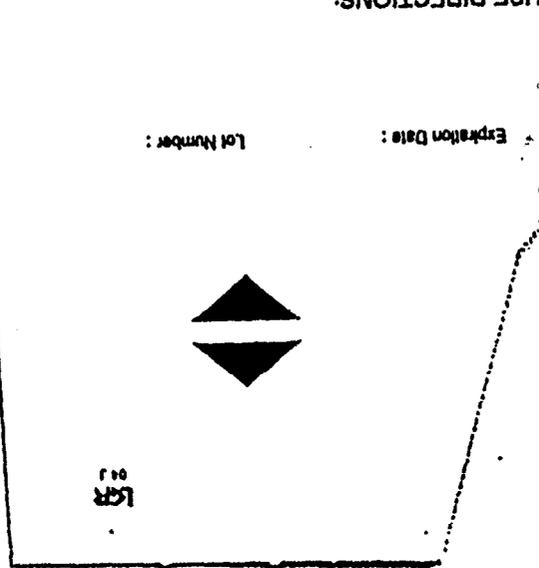
Box of 10 x 10 Cartridge Implants

Manufactured by a non-sterilizing process

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Revalor®-IS Registered trademark HOECHST ROUSSEL VET

Hoechst Roussel Vet



USE DIRECTIONS:

See enclosed package insert.

WARNING:

Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for use in Humans. Implant pellets in the ear only. Any other location is in violation of Federal law. Do not attempt salvage of implanted site for human or animal food.

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NDC 12 799-811-01

Revalor®-IS

(Trenbolone acetate and estradiol)



FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

NET CONTENTS :

Box of 10 x 100 doses packages.

STORAGE CONDITIONS :

Store in a refrigerator (2-8 °C ; 36-47 °F) and protect from sunlight.
Use before the expiration date printed below and on the cartridge.

WARNING :

Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for Use in Humans. Implant pellets in the ear only. Any other location is in violation of Federal Law. Do not attempt salvage of implanted site for human or animal food.

Hoechst Roussel Vet

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Expiration Date

Lot Number

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NDC 12 799-811-01

Revalor®-IS

(Trenbolone acetate and estradiol)



FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

NET CONTENTS :

Box of 4 x 1000 doses packages.

STORAGE CONDITIONS :

Store in a refrigerator (2-8 °C ; 36-47 °F) and protect from sunlight.
Use before the expiration date printed below and on the cartridge.

WARNING :

Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for Use in Humans. Implant pellets in the ear only. Any other location is in violation of Federal Law. Do not attempt salvage of implanted site for human or animal food.

Hoechst Roussel Vet

Made in France by :
Hoechst Roussel Vet

Distributed by:
Hoechst Roussel Vet
Clinton, NJ 08809-4010

Revalor®-IS Registered Trademark Hoechst Roussel Vet

Expiration Date

Lot Number

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OUTER SHIPPING CONTAINER

REVALOR®-IS
(trenbolone acetate and estradiol)

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

STORAGE CONDITIONS:

Store in a refrigerator (2-8°C; 36-47°F) and protect from sunlight.

Made in France by:
Hoechst Roussel Vet

Distributed by:
Hoechst Roussel Vet
Clinton, NJ 08809-4010

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Expiration Date
Lot Number