

Approval Date: _____

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG
APPLICATION

ANADA 200-346

Trenbolone Acetate and Estradiol, and Tylosin Tartrate
(COMPONENT TE-IH with TYLAN)

For increased rate of weight gain for heifers fed in confinement for slaughter.

Supplemental approval to provide for the addition
of a tylosin tartrate pellet as a local antibacterial
to COMPONENT TE-IH

Sponsored by:

Ivy Laboratories
Division of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214

FREEDOM OF INFORMATION SUMMARY

COMPONENT TE-IH with TYLAN Ear Implant for Heifers Fed in Confinement for Slaughter

1. GENERAL INFORMATION:

- a. File Number: ANADA 200-346
- b. Sponsor: Ivy Laboratories
Division of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214
Drug Labeler Code: 021641
- c. Established Names: Trenbolone acetate and estradiol, and tylosin tartrate
- d. Propriety Names: COMPONENT TE-IH with TYLAN
- e. Dosage Form: Implantation (ear implant) as per 21 CFR 522.2477.
- f. How Supplied: Each box contains 5 foil pouches each containing 1 cartridge belt with 20 cells. Each cartridge cell contains 1 implant dose. Each implant dose consists of 4 pellets each containing 20 mg trenbolone acetate and 2 mg estradiol and 1 pellet containing 29 mg tylosin tartrate.
- g. How Dispensed: OTC
- h. Amount of Active Ingredients: Trenbolone acetate: 80 mg trenbolone acetate.
Estradiol: 8 mg estradiol.
Tylosin tartrate: 29 mg tylosin tartrate.
- i. Route of Administration: Subcutaneous ear implant
- j. Species/Class: Heifers fed in confinement for slaughter
- k. Recommended Dosage: One implant containing 80 mg trenbolone acetate, 8 mg estradiol, and 29 mg tylosin tartrate per animal.
- l. Pharmacological Category: Steroid hormone and antibacterial

- m. Indications: For increased rate of weight gain for heifers fed in confinement for slaughter.
- n. Effect of Supplement: This supplement provides for the addition of a tylosin tartrate pellet as a local antibacterial to COMPONENT TE-IH.

2. EFFECTIVENESS:

The effectiveness requirement for this supplemental new animal drug application, with the indication for use and dosage as given in Section 1 above, is met by utilizing the information contained in the Freedom of Information (FOI) Summary for the abbreviated new animal drug application for COMPONENT TE-H (ANADA 200-346) which was approved September 27, 2002, and contains adequate data from a well-controlled study included in this supplemental application.

Title of Study: Tylosin Tartrate Pellet Efficacy/Induction Study Number: Ivy A1076

A study was conducted by William Barton, CAVL, Inc, Amarillo, TX to evaluate the effectiveness of COMPONENT TE-H with TYLAN (140 mg trenbolone acetate and 14 mg estradiol (7 pellets), and 29 mg tylosin tartrate (1 pellet)) to lower the incidence of ear abscess formation. An implant site abscess induction model was developed to reliably create a high abscess rate in test animals. This model was used to test the ability of a tylosin tartrate pellet to reduce implant site abscess incidence in animals expected to develop an ear abscess. In the study, 40 beef heifers were subjected to the abscess-inducing culture at the same time they were implanted with either COMPONENT TE-H with a TYLAN pellet or COMPONENT TE-H alone. Implant sites were observed at regular intervals up to 35 days following implantation. Abscess rate at each time point was significantly lower ($P < 0.0001$) in animals treated with COMPONENT TE-H with a TYLAN pellet compared to animals treated with COMPONENT TE-H alone, with the maximum incidence of abscesses of 5% and 100%, respectively.

3. TARGET ANIMAL SAFETY:

Target animal safety of COMPONENT TE-IH is established by data in the FOI Summary for the parent application (ANADA 200-346) approved September 27, 2002. The data provided in the effectiveness study described above were sufficient to conclude that the use of the tylosin tartrate pellet was safe for use in cattle. No further studies were required.

4. HUMAN SAFETY:

Human safety is established for COMPONENT TE-IH by data in the FOI Summary in the parent application (ANADA 200-346) which was approved September 27, 2002. No further residue studies were required for use of the tylosin tartrate pellet.

A. Microbial Food Safety

The Agency evaluated the microbial food safety for COMPONENT TE-IH ear implants containing 80 mg trenbolone acetate, 8 mg estradiol, and 29 mg of tylosin. The sponsor submitted a microbial food safety “hazard identification” for review. This “hazard identification” information addressed drug-specific characteristics, information on bacterial resistance, and data gaps and emerging science relative to antimicrobial resistance and the use of tylosin in cattle. Upon review of this information, the Agency concluded that use of this product in cattle does not contribute significantly to the emergence or selection of macrolide resistant bacteria of public health concern.

5. AGENCY CONCLUSIONS:

This supplemental ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that trenbolone acetate and estradiol, and tylosin tartrate (COMPONENT TE-IH with TYLAN), when used under its proposed conditions of use, is safe and effective for its labeled indications.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions are accompanied by pictorial diagrams and detailed instructions in plain language. The drug is not a controlled substance. Thus, the product is assigned OTC status, and the labeling is adequate for the intended use.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this supplemental approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval, the basis for which is Ivy Study #A1076, described in Section 2 above. The three years of marketing exclusivity applies only to the addition of the tylosin tartrate pellet as a local antibacterial for which this supplement was approved.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change. 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.

COMPONENT TE-IH with TYLAN is under the following U.S. patent number:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
5,874,098	May 28, 2017

6. ATTACHMENTS:

Facsimile Generic Labeling is attached as indicated below:

COMPONENT TE-IH with TYLAN Box Label
COMPONENT TE-IH with TYLAN 20 Dose Foil Pouch Label (Front)
COMPONENT TE-IH with TYLAN 20 Dose Foil Pouch Label (Back)
COMPONENT TE-IH with TYLAN Package Insert (Front)
COMPONENT TE-IH with TYLAN Package Insert (Back)

COMPONENT[®]

TE-IH

trenbolone acetate 80 mg and estradiol USP 8 mg with 29 mg tylosin tartrate as a local antibacterial
FOR HEIFERS FED IN CONFINEMENT FOR SLAUGHTER

Use With Gray Component One Gun[®] Only

01 20 03 00

COMPONENT TE-IH with Tylan is covered by U.S. Patent No. 5,874,098.
COMPONENT and COMPONENT One Gun are registered trademarks of Ivy Animal Health, Inc.
Tylan is a registered trademark of Eli Lilly and Company.
Manufactured for **VetLife** by Ivy Laboratories • Overland Park, KS 66214, USA
VetLife and Ivy Laboratories are divisions of Ivy Animal Health, Inc.

Important: Read the enclosed instruction brochure. Use as illustrated with a CAREFUL CLEAN TECHNIQUE.
Never take short cuts at the expense of CLEANLINESS.

Note: Studies have demonstrated that administration of COMPONENT[®] TE-IH can result in decreased marking scores when compared to non-implanted heifers.

WARNING: Not to be used in animals intended for subsequent breeding, or in dairy animals. Implant one dose — 5 pellets (entire contents of one cartridge cell) — in the ear subcutaneously. Any other site of implantation is in violation of Federal Law. DO NOT attempt to salvage implantation site for animal feed or human food.



100 IMPLANTS

Patented by Ivy Animal Health, Inc. (MVA 2003) Approved by FDA

Dosage: Administer 1 implant per animal. (See package insert for detailed instructions.)

Content: Each implant contains 5 pellets (entire contents of one cartridge cell) with 80 mg trenbolone acetate, 8 mg estradiol USP, and 29 mg tylosin tartrate as a local antibacterial.

CAREFUL CLEAN TECHNIQUE: The contents of the implant should be used in a clean environment. Do not touch the implant with your hands. Wash hands thoroughly before and after handling the implant.



trenbolone acetate 80 mg and estradiol USP 8 mg with 29 mg tylosin tartrate as a local antibacterial

COMPONENT[®] TE-IH
BRAND IMPLANTS
FOR HEIFERS FED IN CONFINEMENT FOR SLAUGHTER

Manufactured by a non-sterilizing process.

Storage Conditions: Store in a refrigerator (2°-8°C; 36°-46°F) and protect from sunlight.
Use before the expiration date.

**RESTRICTED DRUG — USE ONLY AS DIRECTED (CALIFORNIA) — FOR USE IN ANIMALS ONLY
NOT FOR HUMAN USE — KEEP OUT OF REACH OF CHILDREN**

Use With Gray Component One Gun[®] Only



3.125"

1/4" Seal Area

COMPONENT[®] T-IH
 BRAND IMPLANTS
 trenbolone acetate 80 mg and
 estradiol USP 8 mg with 29 mg
 tylosin tartrate as a local antibacterial

FOR HEIFERS FED IN
 CONFINEMENT FOR
 SLAUGHTER



CONTAINS: One Cartridge. Each of 20 implants sealed in a unitary, hermetic
 container. Each implant contains a reservoir of active ingredients and a delivery system.
 Contains: One Cartridge. Each of 20 implants sealed in a unitary, hermetic
 container. Each implant contains a reservoir of active ingredients and a delivery system.

Dosage: Administer 1 implant per animal. The package insert for detailed information.

Manufactured by a non-sterilizing process.

Patented by the Animal Health Division, Merial, Inc. (Merial, Inc. is a division of Ceva Animal Health, Inc.)

One 20 Dose Cartridge Belt

9.5"

18.875"

18.875"

TEAR HERE

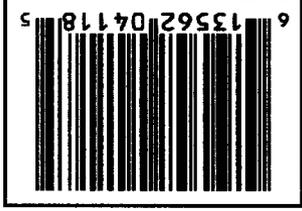
WARNING: Not to be used in animals intended for subsequent breeding, or in dairy animals. Implant one dose — 5 pellets (entire contents of one cartridge cell) — in the ear subcutaneously. Any other site of implantation is in violation of Federal Law. DO NOT attempt to salvage implantation site for animal feed or human food.

**RESTRICTED DRUG — USE ONLY AS DIRECTED (CALIFORNIA) — FOR USE IN ANIMALS ONLY
NOT FOR HUMAN USE — KEEP OUT OF REACH OF CHILDREN**

Note: Studies have demonstrated that administration of Component[®] TE-1H can result in decreased marbling scores when compared to non-implanted heifers.

Important: Read the enclosed instruction brochure. Use as illustrated with a **CAREFUL CLEAN TECHNIQUE.** Never take short cuts at the expense of **CLEANLINESS.**
Storage Conditions: Store in a refrigerator (2°-8°C; 36°-46°F) and protect from sunlight. Use before the expiration date.

COMPONENT is a registered trademark of Ivy Animal Health, Inc.
Tylan is a registered trademark of Eli Lilly and Company.
Manufactured for **VetLife** by Ivy Laboratories • Overland Park, KS 66214, USA
VetLife and Ivy Laboratories are divisions of Ivy Animal Health, Inc.
01 20 02 00



PURCHASE SEAL 20 IMPLANTS

LOT

EXP

9.375"

GENES 1999032



BACK

COMPONENT[®]
BRAND IMPLANTS

VetLife

TE-IH WITH Tylan[®]

FOR HEIFERS FED IN
CONFINEMENT FOR SLAUGHTER

trenbolone acetate 80 mg and
estradiol USP 8 mg with
29 mg tylosin tartrate as a local antibacterial



20-dose Cartridge Belt*

For use with the COMPONENT One Gun**
For Use In Animals Only

Each CARTRIDGE BELT holds 20 doses of COMPONENT[®] TE-IH with Tylan Implants. Each dose of 5 pellets consists of 4 pellets containing a total of 80 mg of trenbolone acetate and 8 mg estradiol plus 1 pellet containing 29 mg tylosin tartrate as a local antibacterial. COMPONENT[®] TE-IH Implants are recommended for use in heifers fed in confinement for slaughter for INCREASED RATE OF WEIGHT GAIN.

INDICATIONS FOR USE: This product contains trenbolone acetate and estradiol for increased rate of weight gain in a slow-release delivery system

NOTE: Studies have demonstrated that administration of COMPONENT[®] TE-IH can result in decreased marbling scores when compared to non-implanted heifers.

DOSAGE: Administer 1 implant per animal according to the following instructions

GENERAL INSTRUCTIONS: Study the instructions which should be followed carefully at all times, avoiding short cuts. Skin infection can be avoided by properly preparing implant site and implanter. During fly season use fly repellent on implant site. One designated team member should always do the implanting. Cleanliness of hands and instruments is important at all times

WARNING

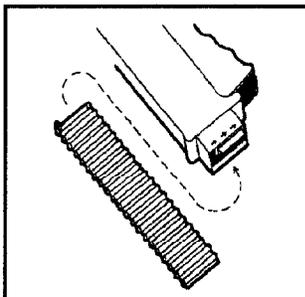
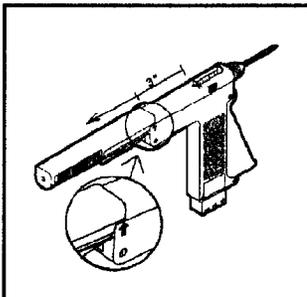
Not to be used in animals intended for subsequent breeding, or in dairy animals. Implant one dose — 5 pellets (entire contents of one cartridge cell) — in the ear subcutaneously. Any other site of implantation is in violation of Federal Law. DO NOT attempt to salvage implantation site for animal feed or human food

**RESTRICTED DRUG – USE ONLY AS DIRECTED (CALIFORNIA) –
FOR USE IN ANIMALS ONLY – NOT FOR HUMAN USE – KEEP OUT OF
REACH OF CHILDREN**

IMPLANTING INSTRUCTIONS:

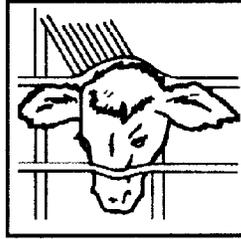
Loading the Implanter

Load the Implanter following the instructions supplied with each Implanter.



Restrain the Animal

Speed of implantation as well as safety of handlers is best achieved by restraining animal in a squeeze chute using head restraint. When implanting horned cattle, better control is obtained with additional use of nose tongs.



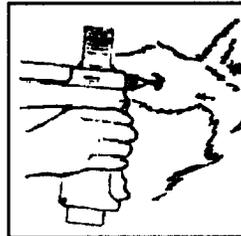
Prepare the Implant Site

Scrub the back side of the ear (implant site) with a piece of clean absorbent cotton which has been soaked with topical germicidal solution. Follow manufacturer's directions on germicide for correct strength and preparation of solution. Avoid getting in animal's eyes.



Where to Implant

The full contents of the cartridge should be implanted beneath the skin on the back side of the middle one-third of the ear illustrated in the drawing. **The implant must not be closer to the head than the edge of the auricular cartilage ring farthest from the head.** The location for insertion of the needle is a point toward the tip of the ear at least a needle length away from the intended deposition site. Avoid injuring the large arteries, veins and cartilage of the ear.



Insert the Needle

With one hand firmly grasp the ear. With the other hand insert needle point through the skin and ease forward on a lateral plane until the entire length of the needle is under the skin.

Implant the Pellets

After inserting the needle fully in the correct implant position squeeze the trigger fully. As the needle is withdrawn from the ear, the controlled-pressure plunger action properly deposits the implant in the needle track. This procedure should prevent breakage or crushing of pellets if otherwise forced into contact with tough fibrous-tissue underlying the skin. The length and total contact area of a single dose are designed to permit absorption of the hormones after implantation to stimulate good weight gain. Broken or crushed pellets may interfere with rates of gain.

Clean the Needle

Clean the implanter needle with alcohol or a properly diluted germicidal solution prior to implanting the next animal.

Storage Conditions

Store in a refrigerator (2°-8°C; 36°-46°F) and protect from sunlight. Use before the expiration date printed on the foil pouch.

ANADA 200-346, Approved by FDA

Manufactured by a non-sterilizing process.

*U.S. Patent No. 4,531,938

**U.S. Patent Nos. 4,762,515 and 5,522,797 – Ivy Animal Health, Inc.

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