

HFA-305  
Div. Dockets Mgmt

Approval Date: 01/11/2011

**FREEDOM OF INFORMATION SUMMARY**  
**ORIGINAL NEW ANIMAL DRUG APPLICATION**

**NADA 141-040**

**Estradiol Benzoate**

**Celerin™**  
**Microencapsulated Estradiol Benzoate**  
**Suspension Implant**

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

**Sponsored by:**

**PR Pharmaceuticals, Inc.**  
**1716 Heath Parkway**  
**Fort Collins, Colorado 80524**

**NADA 141-040**

**FOIS**

1.	<b>GENERAL INFORMATION .....</b>	<b>1</b>
2.	<b>EFFECTIVENESS.....</b>	<b>2</b>
3.	<b>TARGET ANIMAL SAFETY .....</b>	<b>5</b>
4.	<b>HUMAN SAFETY .....</b>	<b>9</b>
5.	<b>AGENCY CONCLUSIONS.....</b>	<b>12</b>
6.	<b>ATTACHMENTS .....</b>	<b>13</b>

## FREEDOM OF INFORMATION SUMMARY

### **Celerin™ (estradiol benzoate) Microencapsulated Estradiol Benzoate Suspension Implant**

#### **1. GENERAL INFORMATION:**

- a. File Number: NADA 141-040
- b. Sponsor: PR Pharmaceuticals, Inc.  
1716 Heath Parkway  
Fort Collins, Colorado 80524  
  
Drug Labeler Code: 067210
- c. Established Name: Estradiol benzoate
- d. Proprietary Name: Celerin™
- e. Dosage Form: Suspension implant
- f. How Supplied: Each package contains one vial of microencapsulated estradiol benzoate powder and one vial of sterile diluent for suspension. The entire package constitutes 50 X 20 mg doses of estradiol benzoate.
- g. How Dispensed: OTC
- h. Amount of Active Ingredients: One mL dose contains 20 mg estradiol benzoate.
- i. Route of Administration: Subcutaneous injection in the ear only. A 16 to 20 gauge needle is recommended.
- j. Species/Class: Steers and heifers fed in confinement for slaughter. Do not use in veal calves, calves intended for reproduction, or calves less than 30 days old.

- k. Recommended Dosage: For improved feed efficiency in steers and heifers and increased rate of weight gain in heifers, administer 20 mg (1mL) of estradiol benzoate.
- For increased rate of weight gain in steers, administer 10 mg (0.5 mL) of estradiol benzoate. The use of 20 mg (1 mL) in steers does not provide additional rate of weight gain improvement over 10 mg (0.5 mL).
- l. Pharmacological Category: Steroid hormone
- m. Indications: For increased rate of weight gain and improved feed efficiency in steers and heifers fed in confinement for slaughter.

## 2. EFFECTIVENESS:

### A. Dosage Characterization:

Dose titration was performed as part of the effectiveness study (see section 2.B below).

### B. Substantial Evidence:

The new animal drug application for Celerin™ (estradiol benzoate) contains data from an adequate and well-controlled investigation demonstrating the effectiveness of the new animal drug for the indications for use and dosage as given in Section 1 above.

Effectiveness of microencapsulated estradiol benzoate was established in a three-location, clinical effectiveness/dose titration study. A uniform protocol was used by each site to allow pooled summary and analysis of study data. Research was conducted in major beef producing areas of the United States.

### Name and Address of Investigators:

Dr. Edward Johnson  
Johnson Research  
Parma, ID 83660

Dr. David Bechtol  
Agri-Research Center, Inc.  
Canyon, TX 79015

Dr. Mary I. Wray  
Horton Feedlot and Research Ctr.  
Wellington, CO 80549

The objective was to determine the dose response for microencapsulated estradiol benzoate (MEB) with lactide/glycolide polymer on rate of weight gain and feed efficiency of steers and heifers fed in confinement for slaughter. The test animals were cross-bred animals of English, Exotic, and Zebu beef breeds. At each site, 120 steers and 120 heifers were assigned to pens (8 animals/pen; steers and heifers were maintained in separate pens) and allotted to treatments via a completely randomized design. Each treatment was replicated 3 times (3 pens/treatment) at all three sites. The treatments consisted of 0, 2.5, 5.0, 10, or 20 mg MEB. The steers and heifers weighed approximately 690 (276 kg) and 667 (302 kg) pounds, respectively, when research was initiated. Study duration ranged from 112 and 164 days for heifers, and 140 and 161 days for steers.

Each animal was administered MEB (in 1 mL sterile diluent) via subcutaneous injection on the backside of the mid-ear. Control cattle were not injected. Animals were given MEB once at the initiation of each study.

Average daily gain and feed efficiency data for the steers and heifers are summarized in Tables 1 and 2, respectively, presented by individual study site, and pooled across sites.

**TABLE 1. EFFECTIVENESS AND DOSE RESPONSIVENESS TO MICROENCAPSULATED ESTRADIOL BENZOATE (MEB) OF STEERS FED IN CONFINEMENT FOR SLAUGHTER.**

<b>Locations</b>				
<b>MEB (mg)</b>	<b>Idaho</b>	<b>Texas</b>	<b>Colorado</b>	<b>Pooled LS Means</b>
<b>Average Daily Gain (lbs)</b>				
0	3.54	3.19	2.84	3.18
2.5	3.16	3.22	2.65	3.21
5.0	3.58	3.30	2.85	3.26
10.0	3.69	3.54	3.32	3.46
20.0	3.83	3.54	3.14	3.51
<b>Feed Efficiency (lbs Dry Matter/lb Gain)</b>				
0	6.07	6.84	6.80	6.51
2.5	6.17	6.41	7.10	6.50
5.0	5.99	6.75	7.14	6.44
10.0	6.11	6.27	6.13	6.40
20.0	5.90	6.37	6.30	6.26

**TABLE 2. EFFECTIVENESS AND DOSE RESPONSIVENESS TO MICROENCAPSULATED ESTRADIOL BENZOATE (MEB) OF HEIFERS FED IN CONFINEMENT FOR SLAUGHTER.**

<b>Locations</b>				
<b>MEB (mg)</b>	<b>Idaho</b>	<b>Texas</b>	<b>Colorado</b>	<b>Pooled LS Means</b>
<b>Average Daily Gain (lbs)</b>				
0	2.91	2.89	2.23	2.68
2.5	2.90	2.99	2.23	2.71
5.0	2.84	3.00	2.32	2.72
10.0	2.93	3.09	2.71	2.91
20.0	3.04	2.96	3.02	3.01
<b>Feed Efficiency (lbs Dry Matter/lb Gain)</b>				
0	6.51	7.01	7.76	7.09
2.5	6.55	6.65	7.56	6.92
5.0	6.39	6.94	7.53	6.95
10.0	6.46	6.29	6.77	6.51
20.0	6.08	6.55	5.69	6.11

The data were pooled and subjected to analysis of variance, and to linear plateau modeling to determine the significance of the effect of MEB on average daily gain and feed efficiency. In steers, average daily gain plateaued at 10 mg MEB; feed efficiency increased linearly, with the 20 mg dose being significantly improved over controls ( $P < .05$ ). In heifers, there was a linear response for both average daily gain and feed efficiency with the 20 mg dose being significantly better than controls ( $P < .05$ ) for both variables.

No effect of treatment was seen on either the carcass parameters (yield grade, quality grade, and marbling scores) or the incidence of liver abscesses evaluated at slaughter for both heifers and steers. No treatment-related adverse conditions were reported at any of the sites.

Based on the data cited above, it is concluded that MEB is effective for the indications for use at the dosage as given in Section 1 above.

### **3. TARGET ANIMAL SAFETY:**

#### **A. Target Animal Safety Study**

A target animal safety study was conducted by Dr. Bill C. Clymer, Clymer Research & Consulting, Inc., Amarillo, TX. The purpose of the study was to assess the safety to beef cattle of MEB when injected subcutaneously in the ear.

Forty-eight (24 bulls/24 heifers) crossbred calves of predominantly Angus and Brahman breeds averaging 35 days of age (age range of 5-57 days) and 112 lbs in weight (weight range of 66-156 lbs) were assigned to treatment in a restricted randomized design by weight (restricted by birth date and balanced by gender within treatment).

Treatment consisted of administering either 0 (no injection), 1X (one dose in the left ear), 3X (two doses in left ear and one in right ear), or 5X (same as the 3X treatment plus 2 dose subcutaneously in the right side on the neck) of MEB (one dose = 20 mg/mL MEB). Six bulls and 6 heifers were used per treatment group. The calves were maintained with their dams in a common pasture for the 140-day experiment period. All animals were observed at least twice weekly for general signs of health, including appetite, movement and respiration. The calves were weighed, subjected to physical examination and blood collection, and the ears were clinically evaluated by palpation at 28-day intervals during the test period.

  
**Celerin™**  
 (estradiol benzoate)  
 Microencapsulated Estradiol Benzoate  
 Suspension Implant  
 For Steers and Heifers Fed in Confinement for Slaughter  
 Manufactured by a non-sterilizing process

---

**Description:**  
 Celerin™ (estradiol benzoate) contains estradiol benzoate in Theraphase™ microspheres. The microspheres have been designed to release estradiol benzoate at a controlled rate to increase rate of weight gain and improve feed efficiency.

This package consists of two vials, one vial containing 50-20mg doses of estradiol benzoate microspheres and one vial containing 50mL of diluent

For Use in Animals Only

**Indications:** Celerin™ (estradiol benzoate) is indicated for increase rate of weight gain and improved feed efficiency in steers and heifers fed in confinement for slaughter. Do not use in veal calves, calves intended for reproduction, or calves less than 30 days old.

**Warnings:** Administer the suspension subcutaneously in the ear only. Any other location is in violation of Federal Law. Do not attempt to salvage this site for animal feed or human use.

A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Keep out of reach of children  
 Use only as directed.

65-20500/00/0603 NADA 141-040, Approved by FDA



Manufactured by  
 PR Pharmaceuticals, Inc  
 1716 Health Parkway  
 Fort Collins, Colorado 80524

Read enclosed package insert and use as directed.  
 Store under refrigerated temperatures between 36° and 46°F (2° and 8°C)  
 Avoid heat and direct sunlight  
 Exposure to excessive heat and direct sunlight will damage product integrity.

Lot No :  
 Exp. Date

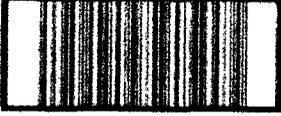
Patent Nos. US 5,288,496 US 5,401,507 US 5,427,796

  
**Celerin™**  
 (estradiol benzoate)

**Microencapsulated Estradiol Benzoate Suspension Implant**  
**For Steers and Heifers Fed in Confinement for Slaughter**  
 Manufactured by a non-sterilizing process

After mixing, Celerin™ suspension is ready to administer. This powder will provide a suspension of Theraphase™ microspheres containing 20mg/mL estradiol benzoate.

Contains 1 gram estradiol benzoate (50-20mg doses),  
 NET WEIGHT 5.0 GRAMS  
 16-00020

  
 659101XXXXXX

**Indications:** Celerin™ (estradiol benzoate) is indicated for increase rate of weight gain and improved feed efficiency in steers and heifers fed in confinement for slaughter. Do not use in veal calves, calves intended for reproduction, or calves less than 30 days old.

**Warnings:** Administer the suspension subcutaneously in the ear only. Any other location is in violation of Federal Law. Do not attempt to salvage this site for animal feed or human use.

A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Keep out of reach of children  
 Use only as directed.

61-500000000603

NDC XXXXXXXXXX

**Celerin**<sup>™</sup>

(estradiol benzoate)

**Microencapsulated Estradiol Benzoate  
Suspension Implant**

For Steers and Heifers Fed in Confinement for Slaughter  
Manufactured by a non-sterilizing process  
50-20 mg doses to be suspended in 50 mL of diluent

NADA 141-040, Approved by FDA

Lot No  
Exp Date

See package insert for mixing and  
use directions. Store under  
refrigerated temperatures between  
36° and 46°F (2° and 8°C).

Manufactured by  
PR Pharmaceuticals, Inc  
1716 Heath Parkway  
Fort Collins, CO 80524

61-501100000603

NDC XXXXXXXXXX

**STERILE DILUENT**

For Use With

**Microencapsulated Estradiol Benzoate  
Suspension Implant**

50 mL for suspension of 50 doses

NADA 141-040, 141-041, Approved by FDA

Lot No  
Exp Date

See package insert for mixing and  
use directions. Store under refrigerated  
temperatures between 36° and 46°F  
(2° and 8°C).

Manufactured for  
PR Pharmaceuticals, Inc  
1716 Heath Parkway  
Fort Collins, CO 80524

NDC XXXXXXXXXX

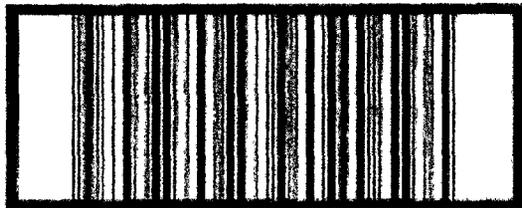


1716 Heath Parkway  
Fort Collins, Colorado 80524

**Celerin™**  
(estradiol benzoate)

Microencapsulated Estradiol Benzoate  
Suspension Implant  
Manufactured by a non-sterilizing process

**20 X 5.0 GRAMS**  
(This case contains 20 units.  
Each unit contains 50 doses  
at 20mg EB per dose)



659101XXXXXX

Store under refrigerated temperatures between 36° and 46° F (2° and 8° C).  
Avoid heat and direct sunlight.

Lot No.:  
Exp. Date:

61-50010/00/0603

NADA 141-041, Approved by FDA

# Celerin™

(estradiol benzoate)

Microencapsulated Estradiol Benzoate  
Suspension Implant

Manufactured by a non-sterilizing process

For Use in Animals Only

**DESCRIPTION:** Celerin™ contains 20mg estradiol benzoate per dose in Theraphase™ microspheres. Each dose consists of a 1mL suspension of the programmed release microspheres. The microspheres have been designed to release estradiol benzoate at a controlled rate in order to increase rate of weight gain and improve feed efficiency.

This package consists of two vials, one vial containing estradiol benzoate microspheres (powder) and one vial containing diluent.

The Celerin™ vial contains estradiol benzoate in 85:15 Poly D,L - Lactide Polymer.

The diluent vial consists of carboxymethylcellulose sodium, USP 2.5%; methylparaben, NF 0.18%; water for injection, USP qs.

Addition of the diluent to the powder results in a suspension ready for use.

**INDICATIONS:** Celerin™ (estradiol benzoate) is indicated for increased rate of weight gain and improved feed efficiency in steers and heifers fed in confinement for slaughter.

**Do not use in veal calves, calves intended for reproduction, or calves less than 30 days old.**

**DOSAGE AND ADMINISTRATION:** Important - Read and follow instructions as illustrated using careful aseptic technique. Never take short cuts at the expense of cleanliness.

Administer 1 dose of the suspension subcutaneously in the ear only. A 16 to 20 gauge needle is recommended. For improved feed efficiency in steers and heifers and increased rate of weight gain in heifers, administer 20mg (1mL) of this suspension.

For increased rate of weight gain in steers, administer 10mg (0.5mL) of the suspension.

**The use of 20mg (1mL) in steers does not provide additional rate of weight gain improvement over 10mg (0.5mL).**

Agitate vial between administration of doses.

Administer the product with a suitable multi-dose syringe.

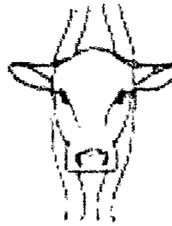
**MIXING INSTRUCTIONS:** Using normal precautions for sterility and safety, draw the entire contents of the liquid diluent into a transfer syringe. Empty contents of transfer syringe into glass vial containing the powder. Mix diluent and powder until all product is suspended. Once mixing has occurred, the suspension should be used within 72 hours. Store under refrigerated temperatures between 36° and 46°F (2° and 8° C). Avoid heat and direct sunlight. Exposure to excessive heat and direct sunlight will damage product integrity.

Do not dose the animal using the transfer syringe or needle.

61-50100/00/0303

## USE INSTRUCTIONS:

NDC XXXXXXXXXX



### Restrain the Animal.

Accuracy of administration as well as safety to handler is best achieved by restraining animal in a squeeze chute using head restraint.

### Prepare the Administration Site.

Scrub the backside of the ear (administration site) using a topical germicidal solution.

### Administration Site.

1 dose should be administered beneath the skin in the backside of the middle one third of the ear as illustrated in the drawing. Location for insertion of the needle is a point near the tip of the ear and a needle length away from the intended deposition site. Avoid injuring the large arteries, veins and cartilage of the ear. Damages to large blood vessels may cause loss of the administered dose.



Diagram of the back of the ear. Note the blood vessels. Avoid injection into vessels. Inject in shaded area.

### Insert the Needle.

Firmly grasp the ear with one hand. With the other hand, insert needle point through the skin and ease forward on a lateral plane until the length of the needle is under the skin. Administer 1 dose.



### Post Administration.

Remove the needle and place thumb on the point of the needle insertion site. Continue to apply pressure as you slide your thumb forward from the point of insertion dispersing the fluid under the skin.

**WARNING:** Administer the suspension subcutaneously in the ear only. Any other location is in violation of Federal Law. Do not attempt to salvage this site for animal feed or human use.

A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Keep out of reach of children.

**ADVERSE REACTIONS:** In clinical studies, no significant adverse reactions were observed.

**PRECAUTION:** Inadvertent intra-arterial injection of solutions intended for subcutaneous injection in the bovine ear may cause sudden death. This effect has not been studied for this product.

Store under refrigerated temperatures between 36° and 46°F (2° and 8° C).

Avoid heat and direct sunlight.

Exposure to excessive heat and direct sunlight will damage product integrity. Suspension should be used within 72 hours.

**HOW SUPPLIED:** Each package contains one vial of microencapsulated estradiol powder and one vial of sterile diluent for suspension. The entire package constitutes 50 X 20 mg doses of estradiol benzoate.

Manufactured by:  
PR Pharmaceuticals, Inc.  
1716 Heath Parkway  
Fort Collins, Colorado 80524

Celerin™ and Theraphase™ are trademarks of PR Pharmaceuticals Inc

© 2003

NADA 141-040, Approved by FDA