

Approval Date: JAN 19 2006

## **FREEDOM OF INFORMATION SUMMARY**

### **SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION**

**NADA 141-040**

**DURALEASE**

**Microencapsulated Estradiol Benzoate  
Suspension Implant  
(Estradiol Benzoate)**

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

This supplement provides for the addition of the suckling beef calf indication "For increased rate of weight gain," originally approved under NADA 141041, to the DURALEASE label. In addition it updates the dosage administration for suckling beef calves to 0.5 mL (10 mg). This supplement also provides for a change in the indication and dosage to allow use for increased rate of weight gain in steers fed in confinement for slaughter, previously at 10 mg (0.5 mL) to 20 mg (1.0 mL). In addition, this supplement also provides for a new 10 mL vial size.

**Sponsored by:**

**PR Pharmaceuticals, Inc.  
1716 Heath Pkwy.  
Fort Collins, CO 80524**

2006-141-040

FOIS 1



|    |                                   |   |
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## FREEDOM OF INFORMATION SUMMARY

### **DURALEASE (estradiol benzoate) Microencapsulated Estradiol Benzoate Suspension Implant**

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

- a. File Number: NADA 141-040
- b. Sponsor: PR Pharmaceuticals, Inc.  
1716 Heath Pkwy.  
Fort Collins, CO 80524  
  
Drug Labeler Code: 067210
- c. Established Name: Estradiol benzoate
- d. Proprietary Name: DURALEASE
- e. Dosage Form: Suspension implant
- f. How Supplied: 50 mL: Each package contains one vial of 1000 mg estradiol benzoate in THERAPHASE microspheres and one 50 mL vial of sterile diluent for suspension. The entire package constitutes 100 x 10 mg doses, or 50 x 20 mg doses of estradiol benzoate.  
  
10 mL: Each package contains one vial of 200 mg estradiol benzoate in THERAPHASE microspheres and one 10 mL vial of sterile diluent for suspension. The entire package constitutes 20 x 10 mg doses, or 10 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 with 45° bevel is

- recommended.
- j. Species/Class: Suckling beef calves and 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 increased rate of weight gain in suckling beef calves administer 0.5 mL (10 mg).  
  
For improved feed efficiency and increased rate of weight gain in steers and heifers, administer 1 mL (20 mg).
- l. Pharmacological Category: Steroid hormone
- m. Indications: For increased rate of weight gain in suckling beef calves and for increased rate of weight gain and improved feed efficiency in steers and heifers fed in confinement for slaughter.
- n. Effect of Supplement This supplement provides for the addition of the suckling beef calf indication "For increased rate of weight gain," originally approved under NADA 141041, to the DURALEASE label. In addition it updates the dosage administration for suckling beef calves to 0.5 mL (10 mg). This supplement also provides for a change in the indication and dosage to allow use for increased rate of weight gain in steers fed in confinement for slaughter, previously at 10 mg (0.5 mL) to 20 mg (1.0 mL). In addition, this supplement also provides for a new 10 mL vial size.

## 2. EFFECTIVENESS:

No new effectiveness data are required for the approval of this supplement. The product's effectiveness in suckling beef calves has been established in the Freedom of Information (FOI) Summary for the parent new animal drug application for CELERIN C (NADA 141041) dated June 25, 2003. The product's effectiveness in steers and heifers fed in confinement for slaughter has been established in the Freedom of Information (FOI) Summary for the parent

new animal drug application for CELERIN (DURALEASE) (NADA 141040) dated June 25, 2003. In the June 25, 2003, approval, increased rate of weight gain in steers fed in confinement for slaughter was approved at the 10 mg estradiol benzoate dose. Since 20 mg was equally effective as 10 mg for increased rate of weight gain in steers, the current supplement also provides for a change in the indication and dosage to allow use for increased rate of weight gain in steers fed in confinement for slaughter at the dose of 20 mg. Since the 10 and 20 mg doses were not statistically different for increased rate of weight gain in steers fed in confinement for slaughter, the DURALEASE label carries the following statement:  
*"Note: In a clinical study evaluating 0, 2.5, 5, 10, and 20 mg of DURALEASE in heifers and steers fed in confinement for slaughter, the 20 mg dose was not different from the 10 mg dose for increased rate of weight gain in steers."*

Improved feed efficiency in steers fed in confinement for slaughter, originally approved at the 20 mg dose, remains in effect.

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

No new target animal safety data are required for the approval of this supplement. The product's target animal safety in steers and heifers fed in confinement for slaughter has been established in the Freedom of Information (FOI) Summary for the parent new animal drug application for CELERIN (DURALEASE) (NADA 141040) dated June 25, 2003. The product's target animal safety in suckling beef calves has been established in the Freedom of Information (FOI) Summary for the parent new animal drug application for CELERIN C (NADA 141041) dated June 25, 2003.

### **4. HUMAN SAFETY:**

No new human food safety data are required for the approval of this supplement. The product's human food safety in steers and heifers fed in confinement for slaughter has been established in the Freedom of Information (FOI) Summary for the parent new animal drug application for CELERIN (DURALEASE) (NADA 141040) dated June 25, 2003. The product's human food safety in suckling beef calves has been established in the Freedom of Information (FOI) Summary for the parent new animal drug application for CELERIN C (NADA 141041) dated June 25, 2003.

### **5. 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 of the implementing regulations. The data demonstrate that estradiol benzoate when administered at 20 mg/mL is safe and effective for the claims indicated in section 1 of this FOI Summary.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

Pursuant to 21 CFR 514.106 (b)(2)(i), this supplemental NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADA.

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

Estradiol benzoate is under the following U.S. patent numbers:

| <u>U.S. Patent Number</u> | <u>Date of Expiration</u> |
|---------------------------|---------------------------|
| 5,288,496                 | February 22, 2011         |
| 5,401,507                 | March 28, 2012            |
| 5,427,796                 | February 22, 2011         |

## **6. ATTACHMENTS:**

Facsimile Labeling is attached as indicated below:

Inner Carton Label (1 x 50 mL)  
Vial Label (DURALEASE – 1000 mg estradiol benzoate  
Vial Label (50 mL sterile diluent)  
Case Shipper Label (10 x 50 mL)  
Package Insert (1 x 50 mL)  
Inner Carton Label (1 x 10 mL)  
Vial Label (DURALEASE – 200 mg estradiol benzoate  
Vial Label (10 mL sterile diluent)  
Case Shipper Label (10 x 10 mL)  
Package Insert (1 x 10 mL)



Label  
4"W x 1.5"H

|  |   |  |  |   |
|--|---|--|--|---|
| 61-80000<br>1020-1832-01<br>Rev. 08-2005                         | Manufactured by<br>PRI Pharmaceuticals, Inc.<br>1735 Health Parkway<br>Fort Collins, CO 80524 | Distributed by<br>Merial Limited<br>2525 Sistrunk Road<br>Macon, GA 30605-4840<br>U.S.A. | Duralease is a trademark<br>of Merial Limited. | <br><b>Microencapsulated Estradiol Benzoate<br/>Suspension Implant</b><br>For Suckling Beef Calves<br>For Steers and Heifers Fed in Confinement for Slaughter<br>Manufactured by a non-sterilizing process<br>Contains 1000 mg of estradiol benzoate<br>to be mixed with 50 mL of diluent for suspension. |
| Lot No.: <input type="text"/><br>Exp. Date: <input type="text"/> |   |  |  | See package insert for mixing and<br>use directions. Store under<br>refrigerated temperatures between<br>36° and 46°F (2° and 8°C).<br>NADA 141-040, Approved by FDA  |

Lot and Exp. area  
1"W x 0.5"H.

|  |  |   |   |  |
|--|--|---|---|--|
| Identification-couleur<br>Project: Duralease<br>GPT# 1020-1832-01<br><br>Merial Spec:<br>Revision(s)-Date:<br>A-05/19/05 BM<br>B-05/21/05 CB<br>C-05/22/05<br>D-09/21/05 PG<br><br> | <b>B</b> <b>PMS 307</b> <b>PMS 326</b>   | <b>Graph. 1</b><br>Nom+Date<br>+Signature :<br><br><input type="checkbox"/> Dieline + Dimensions<br><input type="checkbox"/> Text + Component No.<br><input type="checkbox"/> Specific Codes :<br><input type="checkbox"/> RA Codes <input type="checkbox"/> Barcodes (GMP/UPC)<br><input type="checkbox"/> Product No. <input type="checkbox"/> Merial Address   | <b>Graph. 2</b><br>Nom+Date<br>+Signature :<br><br><input type="checkbox"/> Dieline + Dimensions<br><input type="checkbox"/> Text + Component No.<br><input type="checkbox"/> Specific Codes :<br><input type="checkbox"/> RA Codes <input type="checkbox"/> Barcodes (GMP/UPC)<br><input type="checkbox"/> Product No. <input type="checkbox"/> Merial Address | <b>PRINTED, please read for<br/>SPECIAL INSTRUCTIONS</b><br><br>To print the Merial logo, use the following guide:<br> — PMS 326 + 60% screen of black<br> — PMS 326 |
| <b>Signature pour/Reviewer for<br/>MARKETING*<sub>dpt.</sub></b><br>Nom/Name:<br><br>Date + signature:   | <b>Signature pour/Reviewer for<br/>REGULATORY<sub>int.</sub></b><br>Nom/Name:<br><br>Date + signature: | <b>IMPORTANT NOTES :</b><br><b>IN CASE OF MODIFICATIONS :</b><br><b>EN CAS DE MODIFICATIONS :</b><br><br><b>ONLY READABLE MODIFICATIONS WILL BE<br/>ACCEPTED : Numbered typed texts (word/email)<br/>or numbered "POST-IT" with Acrobat. ( 19 )</b><br><b>SEULES LES MODIFICATIONS LISIBLES SERONT<br/>ACCEPTÉES : Textes saisis numérotés (word/email)<br/>ou "POST-IT" numérotés sous Acrobat. ( 19 )</b><br><br><small>*No approval for registration file submission.<br/>Pas d'approbation pour un dépôt de dossier d'enregistrement.</small> |   |  |
| <b>Signature pour/Reviewer for<br/>PRP REGULATORY</b><br>Nom/Name:<br><br>Date + signature:  | <b>Signature pour/Reviewer for<br/>PRP QUALITY</b><br>Nom/Name:<br><br>Date + signature:               | <b>Signature pour/Reviewer for<br/>PRP PRODUCT MGT</b><br>Nom/Name:<br><br>Date + signature:  |   |  |

Label  
4"W x 1.5"H

|   |   |  |
|---|---|--|
| <p>81-90110<br/>1020-1833-01<br/>Rev. 09-2005</p> <p>Duralesse is a trademark of Merial Limited.</p> <p>Manufactured for:<br/>PFI Pharmaceutical Inc.<br/>7711 Highway 101<br/>Fort Collins, CO 80524</p> <p>Distributed by:<br/>Merial Limited<br/>2235 Saddle Blvd.<br/>Duluth, GA 30085-4940<br/>USA</p> | <p>See package insert for mixing and use directions. Store under refrigerated temperatures between 36° and 46°F (2° and 8°C).</p> | <p><b>STERILE DILUENT</b><br/>For Use With DURALEASE™<br/>Microencapsulated Estradiol Benzoate<br/>Suspension Implant</p> <p>50 mL for suspension</p> <p>NADA 141-040, Approved by FDA</p>  |
| <p>Lot No.: <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px;"></span></p> <p>Exp. Date: <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px;"></span></p>   |   |  |

Lot and Exp area  
1" x 0.6"

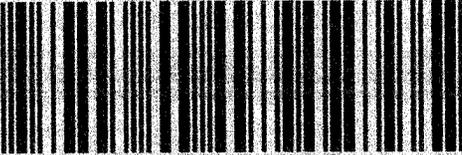
|  |   |  |  |   |
|--|---|--|--|---|
| <p>Identification-couleurs<br/>Project: Duralesse<br/>GPT# 1020-1833-01</p> <p>Merial Spec:<br/>Revision(s)-Date:<br/>A-05/18/05 SM<br/>B-05/18/05 CB<br/>C-05/23/05<br/>D-09/21/05 PQ</p> <p>GPT DULUTH</p> | <p><b>B</b></p>   | <p><b>Graph. 1</b></p> <p>Nom+Date<br/>+Signature :</p> <p><input type="checkbox"/> Dieline + Dimensions<br/><input type="checkbox"/> Text + Component No.<br/><input type="checkbox"/> Specific Codes :</p> <p><input type="radio"/> RA Codes   <input type="radio"/> Barcodes (GMP/UPC)<br/><input type="radio"/> Product No.   <input type="radio"/> Merial Address</p>   | <p><b>Graph. 2</b></p> <p>Nom+Date<br/>+Signature :</p> <p><input type="checkbox"/> Dieline + Dimensions<br/><input type="checkbox"/> Text + Component No.<br/><input type="checkbox"/> Specific Codes :</p> <p><input type="radio"/> RA Codes   <input type="radio"/> Barcodes (GMP/UPC)<br/><input type="radio"/> Product No.   <input type="radio"/> Merial Address</p> | <p><b>PRINTER, please read for<br/>SPECIAL INSTRUCTIONS</b></p> |
| <p>Signature pour/Reviewer for<br/><b>MARKETING<sup>®</sup> dpt.</b></p> <p>Nom/Name:</p> <p>Date + signature:</p>   | <p>Signature pour/Reviewer for<br/><b>REGULATORY<sup>®</sup> dpt.</b></p> <p>Nom/Name:</p> <p>Date + signature:</p> | <p><b>IMPORTANT NOTES :</b><br/>IN CASE OF MODIFICATIONS :<br/>EN CAS DE MODIFICATIONS :</p> <p><b>ONLY READABLE MODIFICATIONS WILL BE ACCEPTED :</b> Numbered typed texts (word/email) or numbered "POST-IT" with Acrobat. (  )</p> <p><b>SEULES LES MODIFICATIONS LISIBLES SERONT ACCEPTÉES :</b> Textes saisis numérotés (word/email) ou "POST-IT" numérotés sous Acrobat. (  )</p> <p><small>*No approval for registration file submission.<br/>Pas d'approbation pour un dépôt de dossier d'enregistrement.</small></p> |  |   |
| <p>Signature pour/Reviewer for<br/><b>PRP REGULATORY</b></p> <p>Nom/Name:</p> <p>Date + signature:</p>   | <p>Signature pour/Reviewer for<br/><b>PRP QUALITY</b></p> <p>Nom/Name:</p> <p>Date + signature:</p>                 | <p>Signature pour/Reviewer for<br/><b>PRP PRODUCT MGT</b></p> <p>Nom/Name:</p> <p>Date + signature:</p>  |  |   |

8-1/2"

4"



**Duralease™**  
(estradiol benzoate)  
Microencapsulated Estradiol Benzoate  
Suspension Implant  
Manufactured by a non-sterilizing process



1 03 50604 416019

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

**Distributed by**  
Merial Limited  
3239 Satellite Blvd.  
Duluth, GA  
30096-4640 U.S.A.

**Item #:** XXXXXX

**CASE:** 10 x 50 mL  
Case contains 10 units.  
Each 50 mL unit contains either:  
50 doses at 20 mg estradiol benzoate/dose  
or 100 doses at 10 mg estradiol benzoate/dose

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

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NADA 141-040, Approved by FDA  
Duralease™ is a trademark of Merial Limited.  
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61-60010  
1025-1836-01  
Rev. 09-2005

Lot No.:

Exp. Date:



|  |   |  |  |  |
|--|---|--|--|--|
| <p>PRP Challenge<br/>PRP 102-855-04</p> <p>Hand No.<br/>Barcode Date<br/>Barcode<br/>Barcode<br/>Barcode</p> <p>See INSTRUCTIONS REVERSED SIDE<br/>for an update on PRP CHALLENGE<br/>requirements prior to next shipment.</p> | <p><b>CRITICAL</b></p> <p>Non-Units<br/>(Quantity)</p> <p><input type="checkbox"/> Initial + Distribution<br/><input type="checkbox"/> Initial + Management Inv.<br/><input type="checkbox"/> Initial + Order<br/><input type="checkbox"/> PRP Order <input type="checkbox"/> Renewal PRP/PO<br/><input type="checkbox"/> Product Inv. <input type="checkbox"/> Initial Address</p> | <p><b>CRITICAL</b></p> <p>Units<br/>(Quantity)</p> <p><input type="checkbox"/> Initial + Distribution<br/><input type="checkbox"/> Initial + Management Inv.<br/><input type="checkbox"/> Initial + Order<br/><input type="checkbox"/> Ah Order <input type="checkbox"/> Renewal PRP/PO<br/><input type="checkbox"/> Product Inv. <input type="checkbox"/> Initial Address</p> | <p><b>SPECIAL INSTRUCTIONS</b></p> <p>14 digit ITF barcode<br/>Program: Barcode Pro 4.0<br/>Barcode type: ITF-14<br/>Magnification (%): 80.71%<br/>Height: 1.25"</p> | <p><b>IMPORTANT NOTES -<br/>IN CASE OF MODIFICATIONS<br/>ENCASE MODIFICATIONS</b></p> <p>ONLY MANUFACTURER MODIFICATIONS WILL BE<br/>ACCEPTED - Rejected labels must be removed<br/>or marked "REJECT" with barcode. (R)<br/>REWORK AND MODIFICATIONS UNLESS<br/>ACCEPTED - Rejected suspension (reworked)<br/>or "REJECT" rework must be marked. (R)<br/>The control of rework is the manufacturer's<br/>responsibility per the applicable regulatory requirements.</p> |
| <p>Manufactured by/Manufacturer for<br/><b>MARKETING</b></p> <p>Hand/Name:</p> <p>Date + signature:</p>  | <p>Manufactured by/Manufacturer for<br/><b>REGULATORY</b></p> <p>Hand/Name:</p> <p>Date + signature:</p>  | <p>Manufactured by/Manufacturer for<br/><b>PRP REGULATORY</b></p> <p>Hand/Name:</p> <p>Date + signature:</p>   | <p>Manufactured by/Manufacturer for<br/><b>PRP QUALITY</b></p> <p>Hand/Name:</p> <p>Date + signature:</p>  | <p>Manufactured by/Manufacturer for<br/><b>PRP PRODUCT NET</b></p> <p>Hand/Name:</p> <p>Date + signature:</p>  |

# Duralease™ (estradiol benzoate)

**Size: 50 mL. Microencapsulated Estradiol Benzoate  
Suspension Implant  
Manufactured by a non-sterilizing process**

### For Use in Animals Only

**DESCRIPTION:** Duralease™ contains 20 mg estradiol benzoate per 1 mL dose or 10 mg per 0.5 mL dose. Each dose consists of a suspension of programmed release Theraphase® 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 Duralease™ 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:** Duralease™ (estradiol benzoate) is indicated for increased rate of weight gain in suckling beef calves and 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. Effectiveness and animal safety in these classes of cattle have not been established.

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

For increased rate of weight gain in suckling beef calves administer 0.5 mL (10 mg).

For improved feed efficiency and increased rate of weight gain in steers and heifers fed in confinement for slaughter, administer 1 mL (20 mg).

Note: In a clinical study evaluating 0, 2.5, 5, 10 and 20 mg of Duralease in heifers and steers fed in confinement for slaughter, the 20 mg dose was not different from the 10 mg dose for increased rate of weight gain in steers.

Administer 1 dose of the suspension subcutaneously in the ear only. A 16 to 20 gauge needle with 45° bevel is recommended.

Agitate the suspension between administration of doses.

Administer the product with a suitable multi-dose syringe.

**MIXING INSTRUCTIONS:** Using normal precautions for sterility and safety, withdraw 50 mL 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.

### USE INSTRUCTIONS:



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



**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.

**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.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Meril at 1-888-637-4251.

**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 1000 mg estradiol benzoate in Theraphase® microspheres and one 50 mL vial of sterile diluent for suspension. The entire package constitutes 100 - 10 mg doses, or 50 - 20 mg doses of estradiol benzoate.

Manufactured by:  
PR Pharmaceuticals, Inc.  
1718 Heath Parkway  
Fort Collins, Colorado 80524

Distributed by:  
Meril Limited  
3239 Satellite Blvd.  
Duluth, GA 30086-4640 U.S.A.

Duralease™ is a trademark of Meril Limited.  
©2005 Meril Limited. All rights reserved.  
Theraphase® is a registered trademark of PR Pharmaceuticals, Inc.



51-60100  
1000-1834-01  
Rev. 08-2005

Item #: 303020X  
NADA 141-040, Approved by FDA  
Patent No's: US 5,284,498 US 5,401,607 US 5,427,796

|  |  |  |
|--|--|--|
| <p>Product/Division<br/>OFF 180-1324-01</p> <p>Animal Spec<br/>Number/Date<br/>Name of Animal<br/>Sex<br/>Age<br/>Breed<br/>Color<br/>Other</p> <p>Use PATIENTS INSTRUCTIONS SYSTEM<br/>for an accurate date of reproduction.<br/>In other circumstances<br/>PATIENTS may be used.</p> | <p>Graph 1<br/>Insert Date<br/>Product 1</p> <p><input type="checkbox"/> Oestrus + Oestrus<br/><input type="checkbox"/> Heat + Oestrus</p> | <p>Graph 2<br/>Insert Date<br/>Product 1</p> <p><input type="checkbox"/> Oestrus + Oestrus<br/><input type="checkbox"/> Heat + Oestrus</p> |
|--|--|--|

**SPECIAL INSTRUCTIONS**

|  |   |  |
|--|---|--|
| <p>Marketing Approval<br/>Name/Name:<br/>Date + signature:</p> | <p>Regulatory Approval<br/>Name/Name:<br/>Date + signature:</p> | <p><b>IMPORTANT NOTES -<br/>IN CASE OF MODIFICATIONS<br/>IN CASE OF MODIFICATIONS</b></p> <p>ONLY READABLE MODIFICATIONS WILL BE<br/>ACCEPTED: (handwritten) (typed) (printed)<br/>or modified "PRINT" with stamp (S)<br/>REUSE USE MODIFICATIONS LEGALLY PROTECT<br/>ACCEPTED: (typed) (printed) (handwritten)<br/>or "PRINT" (handwritten) (typed) (S)<br/>No stamp for signature by administration.<br/>No stamp for signature by administration.</p> |
| <p>PRP REGULATORY<br/>Name/Name:<br/>Date + signature:</p>     | <p>PRP QUALITY<br/>Name/Name:<br/>Date + signature:</p>         | <p>PRP PRODUCT MGT<br/>Name/Name:<br/>Date + signature:</p>  |



Label  
4 1/8" (4.125)W x 1 5/16" (1.3125)H

|  |  |   |   |   |   |
|--|--|---|---|---|---|
| 61-50030<br>1020-2045-00<br>Rev. 09-2005 | Distributed by<br>Merial Limited<br>2230 Statens Blvd.<br>Duluth, GA 30085-4800<br>USA | Distributed by<br>Merial Limited<br>17781 Hamon Parkway<br>Fort Collins, CO 80524 | Manufactured by<br>PRP Pharm Systems, Inc.<br>17781 Hamon Parkway<br>Fort Collins, CO 80524 | See package insert for mixing<br>and use directions. Store under<br>refrigerated temperatures between<br>36° and 46°F (2° and 8°C). | <br><b>Duralease™</b><br>(estradiol benzoate)<br><b>Microencapsulated Estradiol Benzoate<br/>         Suspension Implant</b><br>For Suckling Beef Calves<br>For Steers and Heifers Fed in Confinement for Slaughter<br>Manufactured by a non-sterilizing process<br>Contains 200 mg of estradiol benzoate<br>to be mixed with 10 mL of diluent for suspension.<br>NADA 141-040, Approved by FDA |
| Lot No.: <input type="text"/>            |  | Exp. Date: <input type="text"/>   |   |   |   |

Lot and Exp area  
1" W x 0.5" H

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|---|---|--|---|---|
| Identification-couleurs<br>Project: Duralease<br>GPT# 1020-2045-00<br>Merial Spec:<br>Revision(s)-Date:<br>A-05/27/05 TR<br>B-05/31/05 TR<br>C-09/21/06 PG<br> | <b>B</b> <b>PMS 307</b> <b>PMS 326</b>  | Graph. 1   | Graph. 2  | <b>PRINTER, please read for<br/>         SPECIAL INSTRUCTIONS</b><br>To print the Merial logo, use the following guide:<br> ← PMS 326 + 60% screen of black<br> ← PMS 326 |
|   |   | Norm+Date<br>+Signature :<br><input type="checkbox"/> Dieline + Dimensions<br><input type="checkbox"/> Text + Component No.<br><input type="checkbox"/> Specific Codes :<br><input type="checkbox"/> RA Codes <input type="checkbox"/> Barcodes (GMP/UPC)<br><input type="checkbox"/> Product No. <input type="checkbox"/> Merial Address  | Norm+Date<br>+Signature :<br><input type="checkbox"/> Dieline + Dimensions<br><input type="checkbox"/> Text + Component No.<br><input type="checkbox"/> Specific Codes :<br><input type="checkbox"/> RA Codes <input type="checkbox"/> Barcodes (GMP/UPC)<br><input type="checkbox"/> Product No. <input type="checkbox"/> Merial Address |   |
|   |   | <b>Contrôle GPT</b>  |   |   |
| Signataire pour/Reviewer for<br><b>MARKETING<sup>opt.</sup></b><br>Nom/Name:<br>Date + signature:   | Signataire pour/Reviewer for<br><b>REGULATORY<sup>en.</sup></b><br>Nom/Name:<br>Date + signature: | <b>IMPORTANT NOTES :</b><br><b>IN CASE OF MODIFICATIONS :</b><br><b>EN CAS DE MODIFICATIONS :</b><br><b>ONLY READABLE MODIFICATIONS WILL BE ACCEPTED :</b> Numbered typed texts (word/email) or numbered "POST-IT" with Acrobat. (  )<br><b>SEULES LES MODIFICATIONS LISIBLES SERONT ACCEPTEES :</b> Textes saisis numérotés (word/email) ou "POST-IT" numérotés sous Acrobat. (  )<br><small>*No approval for registration file submission.<br/>         Pas d'approbation pour un dépôt de dossier d'enregistrement.</small> |   |   |
| Signataire pour/Reviewer for<br><b>PRP REGULATORY</b><br>Nom/Name:<br>Date + signature:   | Signataire pour/Reviewer for<br><b>PRP QUALITY</b><br>Nom/Name:<br>Date + signature:              | Signataire pour/Reviewer for<br><b>PRP PRODUCT MGT</b><br>Nom/Name:<br>Date + signature:   |   |   |

Label  
4 1/8" (4.125)W x 1 5/16" (1.3125)H

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| 61-50120<br>1020-2046-00<br>Rev. 09-2005 | Distributed by<br>Merial Limited<br>2525 Slaters Blvd.<br>Darien, GA 30098-4640<br>USA<br>Duralease is a trademark<br>of Merial Limited. | Manufactured for<br>PRP Pharmaceuticals, Inc.<br>1710 South Phoenix<br>Fort Collins, CO 80524 | See package insert for mixing and<br>use directions. Store under<br>refrigerated temperatures between<br>36° and 48°F (2° and 8°C). | <h2>STERILE DILUENT</h2> <p>For Use With DURALEASE™<br/>Microencapsulated Estradiol Benzoate<br/>Suspension Implant</p> <p>10 mL for suspension</p> <p>NADA 141-040, Approved by FDA</p>  |
| Lot No.: <input type="text"/>            |  | Exp. Date: <input type="text"/>   |   |  |

Lot and Exp. area  
1" x 0.5"

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| Identification-couleurs<br>Project: Duralease<br>GPT# 1020-2046-00<br><br>Merial Spec:<br>Revision(s)-Date:<br>A-06/27/05 TR<br>B-05/31/06 TR<br>C-08/21/06 PG<br><br> GPT DULUTH | <b>B</b> | <b>Graph. 1</b>  | <b>Graph. 2</b>  | <b>PRINTER, please read for<br/>SPECIAL INSTRUCTIONS</b> |
|  |          | Nom+Date<br>+Signature :<br><br><input type="checkbox"/> Dieline + Dimensions<br><input type="checkbox"/> Text + Component No.<br><input type="checkbox"/> Specific Codes :<br><input type="checkbox"/> RA Codes <input type="checkbox"/> Barcodes (GMP/UFC)<br><input type="checkbox"/> Product No. <input type="checkbox"/> Merial Address | Nom+Date<br>+Signature :<br><br><input type="checkbox"/> Dieline + Dimensions<br><input type="checkbox"/> Text + Component No.<br><input type="checkbox"/> Specific Codes :<br><input type="checkbox"/> RA Codes <input type="checkbox"/> Barcodes (GMP/UFC)<br><input type="checkbox"/> Product No. <input type="checkbox"/> Merial Address |  |

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| Signataire pour/Reviewer for<br><b>MARKETING</b> dpt.<br>Nom/Name:<br><br>Date + signature: | Signataire pour/Reviewer for<br><b>REGULATORY</b> dpt.<br>Nom/Name:<br><br>Date + signature: |  <b>IMPORTANT NOTES :</b><br><b>IN CASE OF MODIFICATIONS :</b><br><b>EN CAS DE MODIFICATIONS :</b><br><br><b>ONLY READABLE MODIFICATIONS WILL BE<br/>ACCEPTED :</b> Numbered typed texts (word/email)<br>or numbered "POST-IT" with Acrobat. (  )<br><b>SEULES LES MODIFICATIONS LISIBLES SERONT<br/>ACCEPTÉES :</b> Textes saisis numérotés (word/email)<br>ou "POST-IT" numérotés sous Acrobat. (  )<br><br><small>*No approval for registration file submission<br/>Pas d'approbation pour un dépôt de dossier d'enregistrement.</small> |
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| Signataire pour/Reviewer for<br><b>PRP REGULATORY</b><br>Nom/Name:<br><br>Date + signature: | Signataire pour/Reviewer for<br><b>PRP QUALITY</b><br>Nom/Name:<br><br>Date + signature: | Signataire pour/Reviewer for<br><b>PRP PRODUCT MGT</b><br>Nom/Name:<br><br>Date + signature: |
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**Duralease™**  
(estradiol benzoate)

Microencapsulated Estradiol Benzoate  
Suspension Implant

Manufactured by a non-sterilizing process

8-1/2"

4"

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

Distributed by  
Meril Limited  
3239 Satellite Blvd.  
Duluth, GA  
30096-4640 U.S.A.

**Item #: XXXXXX**

**CASE: 10 x 10 mL**  
Case contains 10 units.  
Each 10 mL unit contains either:  
10 doses at 20 mg estradiol benzoate/dose  
or 20 doses at 10 mg estradiol benzoate/dose

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

NADA 141-040, Approved by FDA  
Duralease™ is a trademark of Meril Limited.  
©2005 Meril Limited. All rights reserved.

61-50035  
1025-2048-00  
Rev. 09-2005

Lot No.: \_\_\_\_\_  
Exp. Date: \_\_\_\_\_



XXXXXX XXXXXX



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| <p>Project: Duralease<br/>GPIF 1025-2048-00</p> <p>Meril Spec:<br/>Revision(s): Date:<br/>ADDRESS TO:<br/>4-50035/05<br/>0-50035/05</p> | <p><b>B</b></p> | <p>Graph 1<br/>Norm+Data<br/>+Signature :</p> <p><input type="checkbox"/> Dieline + Dimensions<br/><input type="checkbox"/> Text + Component No.<br/><input type="checkbox"/> Specific Codes :</p> <p><input type="checkbox"/> RA Codes    <input type="checkbox"/> Barcodes (GPI/UPC)<br/><input type="checkbox"/> Product No.   <input type="checkbox"/> Meril Address</p> | <p>Graph 2<br/>Norm+Data<br/>+Signature :</p> <p><input type="checkbox"/> Dieline + Dimensions<br/><input type="checkbox"/> Text + Component No.<br/><input type="checkbox"/> Specific Codes :</p> <p><input type="checkbox"/> RA Codes    <input type="checkbox"/> Barcodes (GPI/UPC)<br/><input type="checkbox"/> Product No.   <input type="checkbox"/> Meril Address</p> | <p><b>14 digit ITF barcode</b><br/>Program: Barcode Pro 4.0<br/>Barcode type: ITF-14<br/>Magnification (%): 80.71%<br/>Height: 1.25"</p> |
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|---|--|---|
| <p>Signature pour/Reviser for<br/><b>MARKETING</b></p> <p>Nom/Name:<br/>Date + signature:</p> | <p>Signature pour/Reviser for<br/><b>REGULATORY</b></p> <p>Nom/Name:<br/>Date + signature:</p> | <p><b>IMPORTANT NOTES :</b><br/>IN CASE OF MODIFICATIONS :<br/>EN CAS DE MODIFICATIONS :</p> <p>ONLY READABLE MODIFICATIONS WILL BE<br/>ACCEPTED : Numbered typed texts (word/email)<br/>or numbered "POST-IT" with Acrobat. ( [ ] )<br/>SEULES LES MODIFICATIONS LISIBLES SERONT<br/>ACCEPTÉES : Textes saisis numérotés (word/email)<br/>ou "POST-IT" numérotés sous Acrobat. ( [ ] )</p> <p><small>*No approval for registration file submission.<br/>Pas d'approbation pour un dépôt de dossier d'enregistrement.</small></p> |
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|--|---|---|
| <p>Signature pour/Reviser for<br/><b>PRP REGULATORY</b></p> <p>Nom/Name:<br/>Date + signature:</p> | <p>Signature pour/Reviser for<br/><b>PRP QUALITY</b></p> <p>Nom/Name:<br/>Date + signature:</p> | <p>Signature pour/Reviser for<br/><b>PRP PRODUCT MGT</b></p> <p>Nom/Name:<br/>Date + signature:</p> |
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# Duralease™ (estradiol benzoate)

**Size: 10 mL. Microencapsulated Estradiol Benzoate  
Suspension Implant  
Manufactured by a non-sterilizing process**

### For Use in Animals Only

**DESCRIPTION:** Duralease™ contains 20 mg estradiol benzoate per 1 mL dose or 10 mg per 0.5 mL dose. Each dose consists of a suspension of programmed release Thersphase® 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 Duralease™ 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:** Duralease™ (estradiol benzoate) is indicated for increased rate of weight gain in suckling beef calves and 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. Effectiveness and animal safety in these classes of cattle have not been established.

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

For increased rate of weight gain in suckling beef calves administer 0.5 mL (10 mg).

For improved feed efficiency and increased rate of weight gain in steers and heifers fed in confinement for slaughter, administer 1 mL (20 mg).

Note: In a clinical study evaluating 0, 2.5, 5, 10 and 20 mg of Duralease in heifers and steers fed in confinement for slaughter, the 20 mg dose was not different from the 10 mg dose for increased rate of weight gain in steers.

Administer 1 dose of the suspension subcutaneously in the ear only. A 16 to 20 gauge needle with 45° bevel is recommended.

Agitate the suspension between administration of doses.

Administer the product with a suitable multi-dose syringe.

**MIXING INSTRUCTIONS:** Using normal precautions for sterility and safety, withdraw 10 mL 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.

### USE INSTRUCTIONS:



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



**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. Damage to large blood vessels may cause loss of the administered dose.

**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 depressing 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.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Meril at 1-866-637-4251.

**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 200 mg estradiol benzoate in Thersphase® microspheres and one 10 mL vial of sterile diluent for suspension. The entire package constitutes 20 - 10 mg doses, or 10 - 20 mg doses of estradiol benzoate.

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

Distributed by:  
Meril Limited  
3238 Satellite Blvd.  
Duluth, GA 30096-4640 U.S.A.

Duralease™ is a trademark of Meril Limited.  
©2005 Meril Limited. All rights reserved.  
Thersphase® is a registered trademark of PR Pharmaceuticals, Inc.



61-60106  
1080-1850-00  
Rev. 06-2005

Item #: 3000002  
NADA 141-040, Approved by FDA  
Patent Nos: US 6,268,498 US 6,401,607 US 6,437,799

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| <p>Product Name: <b>DURALEASE</b></p> <p>Lot Number: <b>1080-1850-00</b></p> <p>Expiry Date: <b>06/2005</b></p> <p>Manufacturer: <b>PR PHARMACEUTICALS, INC.</b></p> <p>Country of Origin: <b>USA</b></p> <p>Regulatory Status: <b>Approved</b></p> <p>Product Code: <b>001</b></p> | <p>Graph 1</p> <p>Insert Date: <b>06/2005</b></p> <p>Insertion Site: <b>Ear</b></p> <p>Insertion Method: <b>Subcutaneous</b></p> <p>Insertion Volume: <b>1 mL</b></p> <p>Insertion Frequency: <b>Once</b></p> <p>Insertion Duration: <b>72 hours</b></p> <p>Insertion Temperature: <b>Refrigerated</b></p> <p>Insertion Location: <b>Backside of ear</b></p> | <p>Graph 2</p> <p>Insert Date: <b>06/2005</b></p> <p>Insertion Site: <b>Ear</b></p> <p>Insertion Method: <b>Subcutaneous</b></p> <p>Insertion Volume: <b>1 mL</b></p> <p>Insertion Frequency: <b>Once</b></p> <p>Insertion Duration: <b>72 hours</b></p> <p>Insertion Temperature: <b>Refrigerated</b></p> <p>Insertion Location: <b>Backside of ear</b></p> | <p>Special Instructions</p> <p>For use in animals only.</p> <p>Do not use in veal calves, calves intended for reproduction, or calves less than 30 days old.</p> <p>Effectiveness and animal safety in these classes of cattle have not been established.</p> <p>Do not use in calves to be processed for veal.</p> |
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| <p><b>MARKETING</b></p> <p>Name/Name:</p> <p>Date + signature:</p>      | <p><b>REGULATORY</b></p> <p>Name/Name:</p> <p>Date + signature:</p>  | <p><b>IMPORTANT NOTES - IN CASE OF MODIFICATIONS:</b></p> <p>ANY SIGNATURE MODIFICATION WILL BE ACCEPTED &amp; RECORDED ONLY IF ACCOMPANIED BY THE FOLLOWING INFORMATION:</p> <p>1. A WRITTEN REQUEST FOR MODIFICATION TO THE PRODUCT NAME OR NAME OF THE MANUFACTURER.</p> <p>2. A WRITTEN REQUEST FOR MODIFICATION TO THE PRODUCT NAME OR NAME OF THE MANUFACTURER.</p> <p>3. A WRITTEN REQUEST FOR MODIFICATION TO THE PRODUCT NAME OR NAME OF THE MANUFACTURER.</p> |
| <p><b>PRP REGULATORY</b></p> <p>Name/Name:</p> <p>Date + signature:</p> | <p><b>PRP QUALITY</b></p> <p>Name/Name:</p> <p>Date + signature:</p> | <p><b>PRP PRODUCT MGT</b></p> <p>Name/Name:</p> <p>Date + signature:</p>  |