

HFA - 305

Stamp Date: AUG 26 2002

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

**ANADA 200-069**

For the treatment of ovarian cysts in dairy cattle.

Sponsored by:

Phoenix Scientific, Inc.  
3915 S. 48<sup>th</sup> Street Terrace  
St. Joseph, MO 64503

F015 1

# FREEDOM OF INFORMATION SUMMARY

## 1. GENERAL INFORMATION:

ANADA Number: 200-069

Sponsor: Phoenix Scientific, Inc.  
3915 South 48<sup>th</sup> Street Terrace  
St. Joseph, MO 64503  
Drug Labeler Code: 059130

Generic Name: gonadorelin diacetate tetrahydrate injection

Trade Name: Fertelin™(Gonadorelin Diacetate  
Tetrahydrate) Sterile Solution

Dosage Form: Injection

How Supplied: 4 mL and 12 mL in glass vials

How Dispensed: Rx

Amount of Active  
Ingredients: 50 mcg gonadorelin/mL

Route of  
Administration: Intravenous or intramuscular injection

Species: Dairy cattle

Pioneer Product/  
"Listed Product": Cystorelin®  
NADA 098-379 (Merial Ltd.)

## 2. INDICATIONS

Fertelin (Gonadorelin) is indicated for the treatment of ovarian follicular cysts in dairy cattle. Ovarian cysts are non-ovulated follicles with incomplete luteinization which result in nymphomania or irregular estrus.

Historically, cystic ovaries have responded to an exogenous source of luteinizing hormone (LH) such as human chorionic gonadotropin. Fertelin initiates release of endogenous LH to cause ovulation and luteinization.

**3. DOSAGE**

The recommended intravenous or intramuscular dosage of Fertelin is 100 mcg/cow.

**4. TARGET ANIMAL SAFETY and DRUG EFFECTIVENESS**

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act, (53 FR 50460, December 15, 1988, First GADPTRA Policy Letter) an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety data, drug effectiveness data, and human food safety data (other than tissue residue data) are not required for approval of an ANADA. An ANADA relies on the target animal safety, drug effectiveness, and human food safety data in the pioneer's new animal drug application. Ordinarily, the ANADA sponsor shows that the generic product is bioequivalent to the pioneer. If bioequivalence is demonstrated through a clinical end-point study, then a tissue residue study to establish the withdrawal time for the generic product is also required. For certain dosage forms, the agency will grant a waiver from conducting an *in vivo* bioequivalence study (55 FR 24645, June 18, 1990: Fifth GADPTRA Policy Letter: Bioequivalence Guideline, October 2000).

Based upon the formulation characteristics of the generic product, Phoenix Scientific, Inc. was granted a waiver from conducting an *in vivo* bioequivalence study for Gonadorelin Injection. The generic and pioneer products contain the same active ingredients in the same concentration and are injections for intravenous or intramuscular administration.

**5. HUMAN FOOD SAFETY:**

**Tolerance**

The tolerances established for the pioneer product apply to the generic product. No tolerances are established for residues of gonadorelin in uncooked edible tissues of cattle.

**Withdrawal Time**

When a waiver from the requirement of an *in vivo* bioequivalence study is granted, the withdrawal times are those previously assigned to the pioneer product. There is a zero-day withdrawal time established for gonadorelin injection.

**Regulatory Methods for Residues**

None

**Human Safety Relative to Possession, Handling and Administration:**

Labeling contains adequate caution/warning statements.

**6. AGENCY CONCLUSIONS:**

This is an Abbreviated New Animal Drug Application filed under section 512(b)(2) of the Federal, Food, Drug and Cosmetic (FFD&C) Act.

Safety and effectiveness for this generic animal drug, Fertelin Sterile Solution, were established by demonstration of chemical equivalence to the pioneer product, Cystorelin® (NADA 098-379), sponsored by Merial Ltd.

This generic product and the pioneer product have identical labeling indications for use in cattle. The route and method of administration of the two drugs are identical. Both drugs are administered by intravenous or intramuscular injection. The generic and pioneer products contain the same active ingredients. Therefore, in compliance with FDA policy promulgated to implement section 512(b)(2) of FFD&C Act, no additional safety, efficacy, or *in vivo* bioequivalency studies were necessary or required.

This ANADA satisfies the requirements of section 512 of the Act and demonstrates that Fertelin Sterile Solution, is safe and effective for its labeled indications when used under the proposed conditions of use.

**Attachments:**

1. **Generic Labeling:**

Package Insert

Vial Labels, 4 mL and 12 mL

2. **Pioneer Labeling**

Package Insert

Vial Label, 10 mL

NDC 59130-689-16

**NET CONTENTS: 4 mL**

**FERTELIN™**  
(Gonadorelin Diacetate Tetrahydrate)

(50 mcg/mL) Sterile Solution  
For Animal Use Only  
Not For Human Use

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**KEEP OUT OF REACH OF CHILDREN**  
ANADA 200-069, Approved by FDA



Model Dose Vial  
Dose: 2 mL (100 mcg)/cow, IV or IM  
See package enclosure for complete directions.

Each mL contains: Gonadorelin diacetate tetrahydrate, 50 mcg; benzyl alcohol, 9 mg; sodium chloride, 7.48 mg and Water for Injection, USP, q.s. pH adjusted with potassium phosphate (monobasic and dibasic).

**STORAGE:** Store between 15°C and 30°C (59°F and 86°F)

600034

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

Manufactured by:  
Phoenix Scientific, Inc.  
St. Joseph, MD 21450

NDC 59130-689-16

**NET CONTENTS: 4 mL**

**FERTELIN™**  
(Gonadorelin Diacetate Tetrahydrate)

(50 mcg/mL) Sterile Solution  
For Animal Use Only  
Not For Human Use

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**KEEP OUT OF REACH OF CHILDREN**  
ANADA 200-069, Approved by FDA



**Multi Dose Vial**  
Dose: 2 mL (100 mcg)/cow, IV or IM  
See package enclosure for complete directions.

Each mL contains: Gonadorelin diacetate tetrahydrate, 50 mcg; benzyl alcohol, 9 mg; sodium chloride, 7.48 mg and Water for Injection, USP, q.s. pH adjusted with potassium phosphate (monobasic and dibasic).

**STORAGE:** Store between 15°C and 30°C (59°F and 86°F)

600034

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

Manufactured by:  
Phoenix Scientific, Inc.  
St. Joseph, MD 21450

*Dec 10/10/97*  
*10/10/97*  
*10-10-97*  
*10/10/97*

**CUSTOMER PROOF • CHECK CAREFULLY!**

Customer:                     PHOENIX SCIENTIFIC                    

P.O. #: \_\_\_\_\_ Date Sent: 2/24/97    3/7/97    3/26/97    10/2/97    10/8/97    \_\_\_\_\_

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Approved by: \_\_\_\_\_

Date approved: \_\_\_\_\_

NDC 59130-689-17

Each mL contains: Gonadorelin diacetate tetrahydrate, 50 mcg; benzyl alcohol, 9 mg; sodium chloride, 7.48 mg and Water for Injection, USP, q.s. pH adjusted with potassium phosphate (monobasic and dibasic).

**FERTELIN™**  
(Gonadorelin Diacetate Tetrahydrate)  
(50 mcg/mL)  
Sterile Solution

For Animal Use Only  
Not For Human Use  
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.  
KEEP OUT OF REACH OF CHILDREN  
ANADA 200-069, Approved by FDA

Multi Dose Vial  
Dose: 2 mL (100 mcg)/cow, IV or IM  
See package enclosure for complete directions.

STORAGE: Store between 15°C and 30°C (59°F and 86°F)

Manufactured by:  
Phoenix Scientific, Inc.  
St. Joseph, MO 64506

600034

Iss. 9-97

AmTech Group, Inc.

NET CONTENTS: 12 mL

Lot No.  
Exp. Date

NDC 59130-689-17

Each mL contains: Gonadorelin diacetate tetrahydrate, 50 mcg; benzyl alcohol, 9 mg; sodium chloride, 7.48 mg and Water for Injection, USP, q.s. pH adjusted with potassium phosphate (monobasic and dibasic).

**FERTELIN™**  
(Gonadorelin Diacetate Tetrahydrate)  
(50 mcg/mL)  
Sterile Solution

For Animal Use Only  
Not For Human Use  
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.  
KEEP OUT OF REACH OF CHILDREN  
ANADA 200-069, Approved by FDA

Multi Dose Vial  
Dose: 2 mL (100 mcg)/cow, IV or IM  
See package enclosure for complete directions.

STORAGE: Store between 15°C and 30°C (59°F and 86°F)

Manufactured by:  
Phoenix Scientific, Inc.  
St. Joseph, MO 64506

600034

Iss. 9-97

AmTech Group, Inc.

NET CONTENTS: 12 mL

Lot No.  
Exp. Date

lc 10/6/97

9/6/97

lc 10/6/97  
07/10/6/97

RG 9-6-91

### CUSTOMER PROOF • CHECK CAREFULLY!

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Approved by: \_\_\_\_\_

Date approved: \_\_\_\_\_

AM

ANADA 200-069, Approved by FDA

**FERTELIN™**  
50 mcg/mL  
(Gonadorelin Diacetate Tetrahydrate)  
**FOR INJECTION**

For the treatment of cystic ovaries in cattle

**CAUTION:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION:** Fertelin is a sterile solution containing 50 micrograms of gonadorelin (GnRH) diacetate tetrahydrate per milliliter suitable for intramuscular or intravenous administration. Gonadorelin is a decapeptide composed of the sequence of amino acids-

5-oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH<sub>2</sub>-  
a molecular weight of 1182.32 and empirical formula C<sub>55</sub>H<sub>75</sub>N<sub>17</sub>O<sub>13</sub>. The diacetate tetrahydrate ester has a molecular weight of 1374.48 and empirical formula C<sub>59</sub>H<sub>91</sub>N<sub>17</sub>O<sub>21</sub>.

Gonadorelin is the hypothalamic releasing factor responsible for the release of gonadotropins (e.g., LH, FSH) from the anterior pituitary. Synthetic gonadorelin is physiologically and chemically identical to the endogenous bovine hypothalamic releasing factor.

**PHARMACOLOGY AND TOXICOLOGY:** Endogenous gonadorelin is synthesized and/or released from the hypothalamus during various stages of the bovine estrus cycle following appropriate neurogenic stimuli. It passes via the hypophyseal portal vessels, to the anterior pituitary to effect the release of gonadotropins (e.g., LH, FSH). Synthetic gonadorelin administered intravenously or intramuscularly also causes the release of endogenous LH or FSH from the anterior pituitary.

Gonadorelin diacetate tetrahydrate has been shown to be safe. The LD<sub>50</sub> for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mcg/kg, respectively. No untoward effects were noted among rats or dogs administered 120 mcg/kg/day or 72 mcg/kg/day intravenously for 15 days.

It has no adverse effects on heart rate, blood pressure, or EKG to unanesthetized dogs at 60 mcg/kg. In anesthetized dogs it did not produce depression of myocardial or system hemodynamics or adversely affect coronary oxygen supply or myocardial oxygen requirements.

The intravenous administration of 60 mcg/kg/day of gonadorelin diacetate tetrahydrate to pregnant rats

and rabbits during organogenesis did not cause embryotoxic or teratogenic effects.

The intramuscular administration of 1000 mcg to normally cycling dairy cattle had no effect on hematology or blood chemistry.

Further, Fertelin does not cause irritation at the site of intramuscular administration in dogs. The dosage administered was 72 mcg/kg/day for seven (7) days.

**INDICATIONS AND DOSAGE:** Fertelin (Gonadorelin) is indicated for the treatment of ovarian follicular cysts in dairy cattle. Ovarian cysts are non-ovulated follicles with incomplete luteinization which result in nymphomania or irregular estrus.

Historically, cystic ovaries have responded to an exogenous source of luteinizing hormone (LH) such as human chorionic gonadotropin. Fertelin initiates release of endogenous LH to cause ovulation and luteinization.

The recommended intravenous or intramuscular dosage of Fertelin is 100 mcg/cow.

Each mL of Fertelin contains:

- Gonadorelin diacetate tetrahydrate . . . . . 50 mcg
  - Benzyl Alcohol . . . . . 9 mg
  - Sodium Chloride . . . . . 7.48 mg
  - Water for Injection, U.S.P. . . . . q.s.
- pH adjusted with potassium phosphate (monobasic and dibasic).

Store between 15°C and 30°C (59°F and 86°F)

**HOW SUPPLIED:** Fertelin is available in a concentration of 50 mcg/mL, pH adjusted with potassium phosphate (monobasic and dibasic).

Fertelin is supplied in multi-dose vials containing 4 mL or 12 mL of sterile solution.

Manufactured by  
Phoenix Scientific, Inc.  
St. Joseph, MO 64506

600034

Iss. 9-97

**CUSTOMER PROOF • CHECK CAREFULLY!**

Customer: PHOENIX SCIENTIFIC

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Approved by: \_\_\_\_\_

Date approved: \_\_\_\_\_

*cc 10/16/97  
at 10/10/97  
re  
2/27/97*

Each mL of Cystorelin contains:

Gonadorelin diacetate tetrahydrate .....	50 mcg
Benzyl Alcohol .....	9 mg
Sodium Chloride .....	7.47 mg
Water for Injection, U.S.P. ....	q.s.

pH adjusted with potassium phosphate (monobasic and dibasic).

**PRECAUTIONS:**

**Not for use in humans.**

**Keep this and all drugs out of reach of children.**

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

**KEEP REFRIGERATED: 2°-8°C (36°-46°F).**

**HOW SUPPLIED:**

Cystorelin is available in a concentration of 50 mcg/mL pH adjusted with potassium phosphate (monobasic and dibasic).

Cystorelin is supplied in multi-dose vials containing 10 mL of sterile solution.

NADA 098-379, Approved by FDA

List No. 8283-03  
C-03004-R3

# CYSTORELIN®

## (Gonadorelin Diacetate Tetrahydrate)

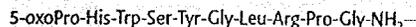
**FOR INJECTION**

**For the treatment of cystic ovaries in cattle**

**CAUTION:** Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION:**

CYSTORELIN is a sterile solution containing 50 micrograms of gonadorelin (GnRH) diacetate tetrahydrate per milliliter suitable for intramuscular or intravenous administration. Gonadorelin is a decapeptide composed of the sequence of amino acids—



a molecular weight of 1182.32 and empirical formula  $C_{55}H_{75}N_{17}O_{13}$ . The diacetate tetrahydrate ester has a molecular weight of 1374.48 and empirical formula  $C_{59}H_{91}N_{17}O_{21}$ .

Gonadorelin is the hypothalamic releasing factor responsible for the release of gonadotropins (e.g., LH, FSH) from the anterior pituitary. Synthetic gonadorelin is physiologically and chemically identical to the endogenous bovine hypothalamic releasing factor.

**PHARMACOLOGY AND TOXICOLOGY:**

Endogenous gonadorelin is synthesized and/or released from the hypothalamus during various stages of the bovine estrus cycle following appropriate neurogenic stimuli. It passes via the hypophyseal portal vessels, to the anterior pituitary to effect the release of gonadotropins (e.g. LH, FSH). Synthetic gonadorelin administered intravenously or intramuscularly also causes the release of endogenous LH or FSH from the anterior pituitary.

Gonadorelin diacetate tetrahydrate has been shown to be safe. The LD<sub>50</sub> for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mcg/kg, respectively. No untoward effects were noted among rats or dogs administered 120 mcg/kg/day or 72 mcg/kg/day intravenously for 15 days.

It has no adverse effects on heart rate, blood pressure, or EKG to unanesthetized dogs at 60 mcg/kg. In anesthetized dogs it did not produce depression of myocardial or system hemodynamics or adversely affect coronary oxygen supply or myocardial oxygen requirements.

The intravenous administration of 60 mcg/kg/day of gonadorelin diacetate tetrahydrate to pregnant rats and rabbits during organogenesis did not cause embryotoxic or teratogenic effects.

The intramuscular administration of 1000 mcg to normally cycling dairy cattle had no effect on hematology or blood chemistry.

Further, Cystorelin does not cause irritation at the site of intramuscular administration in dogs. The dosage administered was 72 mcg/kg/day for seven (7) days.

**INDICATIONS AND DOSAGE:**

CYSTORELIN is indicated for the treatment of ovarian follicular cysts in dairy cattle. Ovarian cysts are non-ovulated follicles with incomplete luteinization which result in nymphomania or irregular estrus.

Historically, cystic ovaries have responded to an exogenous source of luteinizing hormone (LH) such as human chorionic gonadotropin. Cystorelin initiates release of endogenous LH to cause ovulation and luteinization.

The recommended intravenous or intramuscular dosage of Cystorelin is 100 mcg/cow.

Marketed by:  
Merial Limited  
Iselin, NJ 08830-3077

Merial Limited: Registered in England and Wales [Reg. No. 3332751] with registered offices at 27 Knightsbridge, London, SW1X 7QT, England and domesticated in Delaware, USA as Merial LLC.

® Registered trademark of Merial  
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December 2000





**PRECAUTIONS: FOR ANIMAL USE ONLY  
NOT FOR HUMAN USE  
KEEP OUT OF THE REACH OF  
CHILDREN**

**KEEP REFRIGERATED:  
2°-8°C (36°-46°F)**

Marketed by: Merial Limited  
Isefin, NJ 08830-3077

® Registered trademark of Merial.

Exp.:

Lot

List No. 8283-03  
C-03001-R3



**CYSTORELIN®**

(Gonadorelin Diacetate Tetrahydrate)

(50 mcg/mL) Sterile Solution

**CAUTION:** Federal (U.S.A.) law restricts  
this drug to use by or on the  
order of a licensed veterinarian.

NADA 098-379, Approved by FDA

**NET CONTENTS: 20 x 10 mL**



**RECOMMENDED DOSE:** Each mL contains: Gonadorelin diacetate tetrahydrate, 50 mcg; benzyl alcohol, 9 mg; sodium chloride, 7.47 mg and Water for Injection, USP, q.s. pH adjusted with potassium phosphate (monobasic and dibasic).

**KEEP REFRIGERATED: 2°-8°C (36°-46°F)  
PRECAUTIONS: FOR ANIMAL USE ONLY  
NOT FOR HUMAN USE  
KEEP OUT OF THE REACH OF CHILDREN  
Multi-Dose Vial**

See package enclosure for complete directions.  
Marketed by: Merial Limited, Isefin, NJ 08830-3077

® Registered trademark of Merial.

List No. 8283-03  
C-03002-R3

**CYSTORELIN®**

(Gonadorelin Diacetate Tetrahydrate)

(50 mcg/mL) Sterile Solution

**CAUTION:** Federal (U.S.A.) law  
restricts this drug to use by or on  
the order of a licensed veterinarian.

NADA 098-379, Approved by FDA

**NET CONTENTS:  
10 mL**



Exp.:

Lot