New product approval for Fixed-Time AI

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Zoetis Dairy Technical Services

Factrel®
(gonadorelin hydrochloride)
Sterile Solution

Lutalyse®
(dinoprost tromethamine)
Sterile Solution

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More than two years in the making

Veterinary Medicine Research & Development
Pfizer Inc
Kalamazoo, Michigan 49001-0199
United States

Pivotal, Dose Titration, Multi-location, Field Efficacy Study for the Sequential Use of FACTREL® Sterile Solution (gonadorelin hydrochloride) and LUTALYSE® Sterile Solution for Synchronization of Estrous Cycles to Allow Fixed-Time Artificial Insemination in Dairy Cows

STUDY NUMBER:	1930C-60-11-912
PROJECT NAME:	P-Factrel & Lutalyse for Fixed Time AI, US
PROJECT CODE:	7ABDS00000
INAD NUMBER:	011-912
TEST PERMIT OR CERTIFICATE NUMBER:	NA
SUBSTANCE CODE:	CP112410 and PNU14583E
COMPOUND NAME:	Gonadorelin Hydrochloride (GnRH) and Dinoprost tromethamine (prostaglandin $F_{2\alpha}$; $PGF_{2\alpha}$)

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FACTREL® (*gonadorelin hydrochloride)* Sterile Solution is now approved by the Food and Drug Administration (FDA) for use with LUTALYSE® (*dinoprost tromethamine)* Sterile Solution to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.

Opportunity!

- You now have the option to prescribe FDA-approved Zoetis products on label in a manner consistent with many current reproduction management strategies.
- With the new flexible label approval, you and your clients are able to choose from several proven estrous synchronization schedules for fixed-time AI.
- This FDA approval continues Zoetis' more than 60-year history as the animal health business of Pfizer delivering innovations, dedicated service and a commitment to securing additional claims that are safe and effective and that meet the needs of current uses in the marketplace.


HELPING YOU DO
WHAT YOU DO BEST.
Introducing new product approval for fixed-time AI.
We're proud to support the dairy industry and the producers who wake up before the sun rises and work long after it's set. That's why Zoetis has worked for two years to secure the approval for FACTREL® (gonadorelin hydrochloride) Sterile Solution to be used with LUTALYSE® (dinoprost tromethamine) Sterile Solution for fixed-time artificial insemination. The new approval allows you to use products you've trusted and relied on for years. Visit DairyProSolutions.com to learn more.
Factrel®
(gonadorelin hydrochloride)
Sterile Solution
Lutalyse®
(dinoprost tromethamine)
Sterile Solution
Important Safety Information for FACTREL: FACTREL is available through veterinary prescription only and not for use in humans. As with all drugs, FACTREL should not be used in animals found to be hypersensitive to the product. See full prescribing information, on page X.
Important Safety Information for LUTALYSE: As with all parenteral products, aseptic technique should be used to reduce the possibility of post-injection bacterial infections. Do not administer in pregnant animals unless cessation of pregnancy is desired. Not for intravenous administration. Women of childbearing age and persons with respiratory problems should exercise extreme caution when handling this product. See full prescribing information, on page X.
DAIRY WELLNESS MAKES A DIFFERENCE™
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SEQUENTIAL USE OF FACTREL AND LUTALYSE TO ALLOW FIXED-TIME ARTIFICIAL INSEMINATION IN DAIRY COWS

Pivotal Efficacy Study: Goals

- To establish the effectiveness of FACTREL and LUTALYSE for synchronizing estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.
- To establish/confirm the appropriate dose of FACTREL for synchronizing estrous cycles to allow FTAI in lactating dairy cows.
  - Prior label dosage of 100 µg GnRH were indicated for the treatment of cystic ovaries, not for estrous synchronization to allow for FTAI.
  - Is 100 µg of GnRH the appropriate dose for FTAI?

Pivotal Efficacy Study Design: Sites and Cows

- The large, multisite study involved 1,142 Holstein, Jersey and crossbred lactating dairy cows maintained at six commercial dairies in NY, MI, MN, FL, CO, and CA

- A common protocol was conducted at the six study sites
  - Cows were >32 and <140 days post-calving at enrollment (Day 0).
  - Cows were clinically normal at enrollment.
  - Cows had a BCS ≥2 and ≤4.

Allotment to Treatment and Post-enrollment Observations

- Each study site used a control group and three treatment groups.
- Cows were randomly assigned to blocks of four as deemed eligible for enrollment within pen without regard to parity.
- Cows were observed at least once daily for estrus and abnormal clinical signs from Day 1 to completion of study.
- Cows in estrus after Day 12 could be inseminated and were assumed to be not pregnant.
- Final pregnancy diagnosis was conducted at 42 to 65 days post-breeding.

Pivotal Efficacy Study Design: Treatment Groups

- Control group: 5 mL LUTALYSE on Day 7 with fixed-time AI 72 (± 2 hours) later

- Three treatment groups received either 100, 150, or 200 ug GnRH:
  - Day 0: First dose GnRH (FACTREL)
  - Day 7: 5 mL LUTALYSE
  - Day 9: Each site selected to administer the second dose of GnRH at either:
    - 48 (±2 hours) after LUTALYSE with FTAI 24 (±2 hours) later (Day 10) or
    - 56 (±2 hours) after LUTALYSE with FTAI 17 (±2 hours) later (Day 10)

Pregnancy Rate Defined

Primary variable for efficacy – pregnancy rate to FTAI (P/AI)

$$PR = \frac{\text{number pregnant at 42 to 65 days pos-FTAI}}{\text{number of animals enrolled - animals removed from analysis}}$$

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Pivotal Efficacy Study Results: Efficacy

- Pregnancy rates for each treatment group and p-value **comparison with Control**
  - Control = 17.1%
  - FACTREL 2 mL (100 µg GnRH) = 27.3%; p=0.012
  - FACTREL 3 mL (150 µg GnRH) = 29.1%; p=0.005
  - FACTREL 4 mL (200 µg GnRH) = 32.2%; p=0.001

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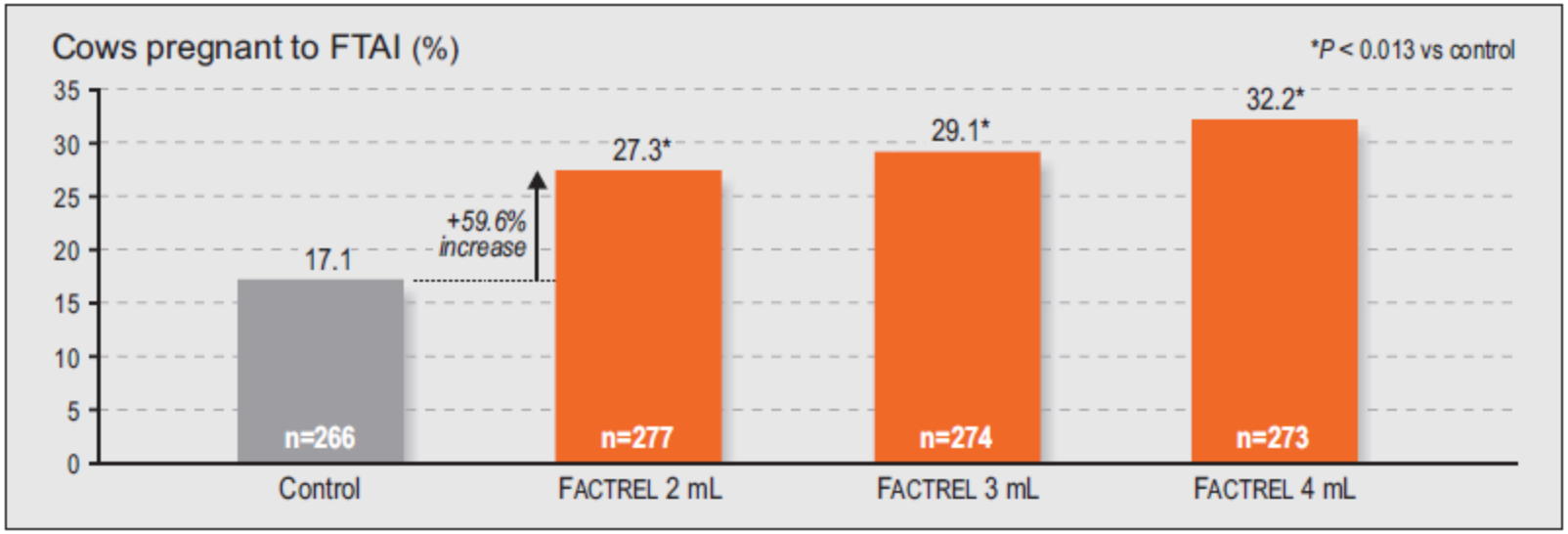
Pivotal Efficacy Study Results: Pregnancy rate of lactating cows to fixed-time AI (FTAI)



Significant differences in pregnancy rates between each great treated with FACTREL compared with the control group, ***not treated with FACTREL.***

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Pivotal Efficacy Study Results: Pregnancy rate of lactating cows to fixed-time AI (FTAI)

- No differences were detected between any of the FACTREL dose groups for pregnancy rate to FTAI
- None of the pair-wise comparisons approached significance (P>0.1)
- For all pair-wise comparisons, P>0.1
  - T02 (2 mL FACTREL) vs. T04 (4 mL FACTREL) p=0.2559
  - T02 (2 mL FACTREL) vs. T03 (3 mL FACTREL) p=0.6677
  - T03 (3 mL FACTREL) vs. T04 (4 mL FACTREL) p=0.4665

The study was designed to have 80% ability to detect a 15 percentage point difference between treatment groups; the greatest difference between these treatment groups was 4.9 percentage points (T02 vs. T04).

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FACTREL: INDICATIONS FOR USE

FACTREL: Indications For Use

DOSAGE

- For the treatment of ovarian follicular cysts in cattle: Administer 2 mL of FACTREL as a single intramuscular injection.
- For use with LUTALYSE to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows: Administer 2 to 4 mL FACTREL (100 – 200 mg gonadorelin) per cow as an intramuscular injection in a treatment regimen with the following framework:
  - Administer the first dose of FACTREL (2 - 4 mL) at Day 0.
  - Administer LUTALYSE (25 mg dinoprost) by intramuscular injection 6 to 8 days after the first dose of FACTREL.

FACTREL: Indications For Use

- Administer a second dose of FACTREL (2 - 4 mL) 30 to 72 hours after the injection of LUTALYSE.
- Perform FTAI 0 to 24 hours after the second dose of FACTREL, or inseminate cows on detected estrus using standard herd practices.

Below are three examples of treatment regimens for FTAI that fit within the dosage regimen framework described immediately above:

	Example 1	Example 2	Example 3
Day 0 (Monday)	1st FACTREL	1st FACTREL	1st FACTREL
Day 7 (the following Monday)	LUTALYSE	LUTALYSE	LUTALYSE
Day 9 (Wednesday)	2nd FACTREL + FTAI at 48 hours after LUTALYSE	2nd FACTREL 48 hours after LUTALYSE	2nd FACTREL 56 hours after LUTALYSE
Day 10 (Thursday)		FTAI 24 hours after 2nd FACTREL	FTAI 18 hours after 2nd FACTREL

Doses of FACTREL Injection greater than 2 mL have not been shown to provide additional benefit on pregnancy rate to FTAI.

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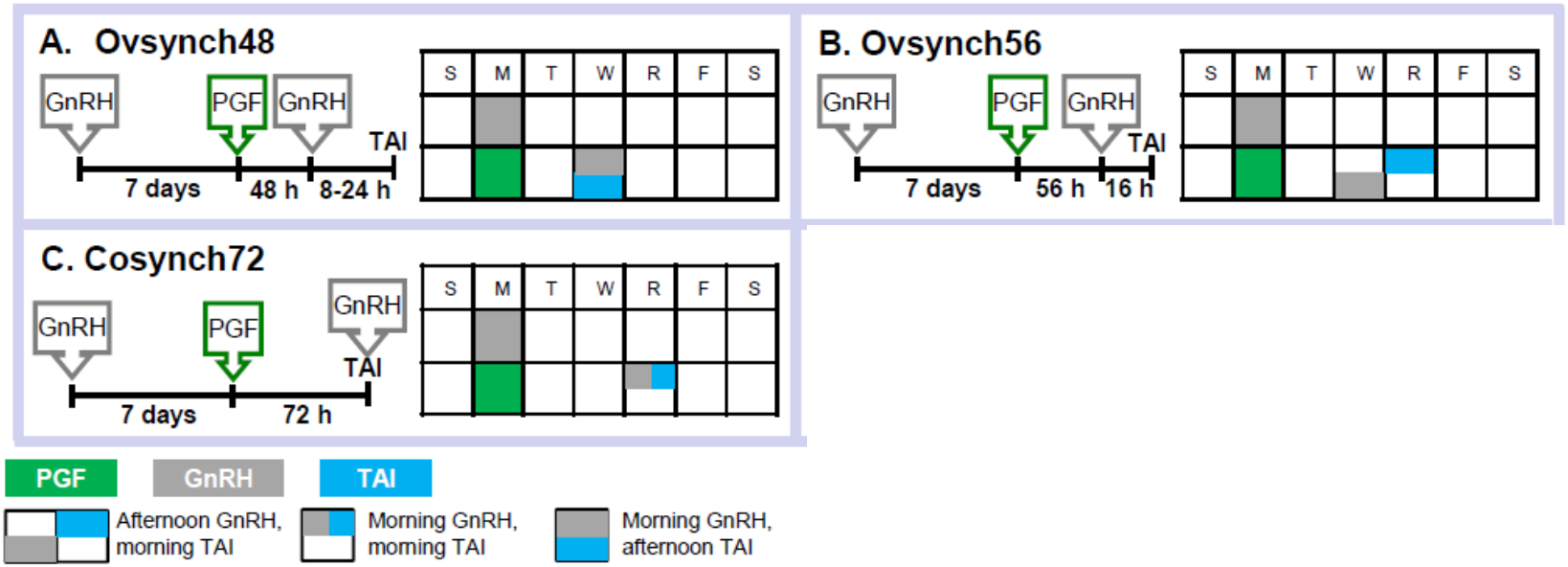
Flexible label fits with many of the DCRC recommended programs for FTAI

Ovsynch methods used for TAI

Can be used alone or with presynch methods (see above). Programs can be used with or without EDAI.



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DCRC Compliance Table

Compliance	3 injection program	5 injection program
100%	100%	100%
95%	86%	77%
90%	73%	59%

This protocol sheet was assembled by members of the Dairy Cattle Reproduction Council (DCRC). Programs are intended to promote sustainable food production by the dairy industry through sound reproductive management practices.

M.C. Lucy (MO) , R.C. Chebel (MN), P.M. Fricke (WI), J.C. Dalton (ID), and S.E. Poock (MO).

Conclusions

- This extensive field study conducted under commercial production conditions demonstrated the effectiveness of using FACTREL with LUTALYSE to synchronize estrous cycles to allow FTAI in lactating dairy cows.
- All doses of FACTREL (2, 3 and 4 mL) resulted in significantly greater pregnancy rates to FTAI compared with the control group.
- The regimens for FACTREL/LUTALYSE evaluated in this study represent substantial advances in reproductive management that allow dairy producers to more reliably synchronize estrus of lactating dairy cows to FTAI.
- For more information, contact your Zoetis representative.

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IMPORTANT SAFETY INFORMATION

- **FACTREL:**FACTREL is available through veterinary prescription only and not for use in humans. As with all drugs, FACTREL should not be used in animals found to be hypersensitive to the product. See full prescribing information, here.

- **LUTALYSE:** As with all parenteral products, aseptic technique should be used to reduce the possibility of post-injection bacterial infections. Do not administer in pregnant animals unless cessation of pregnancy is desired. Not for intravenous administration. Women of childbearing age and persons with respiratory problems should exercise extreme caution when handling this product. See full prescribing information, here.

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Thank You!