LUTALYSE® (dinoprost tromethamine) Sterile Solution has been approved for synchronization of estrus in cattle for more than 30 years. It has been the most widely used prostaglandin product since its launch and is the trusted foundation of breeding programs across the country. Pfizer Animal Health, the makers of LUTALYSE, have invested heavily in research to understand all aspects of the biology and practical use of LUTALYSE under commercial conditions. This has not only furthered understanding of LUTALYSE but also has helped move reproductive management forward within the U.S. dairy industry.

Nonetheless, competitive suppliers have pursued advertising and sales messaging that suggest LUTALYSE is not as efficacious as cloprostenol or does not work under modern conditions. Intervet/Schering-Plough (now known as Merck Animal Health), which markets cloprostenol as Estrumate® (cloprostenol sodium) in the U.S., was the source of this misleading messaging. FDA issued communication Sept. 16, 2010, ordering Intervet/Schering-Plough to immediately cease and desist claims of biological superiority in comparison with LUTALYSE, as these claims have not been demonstrated by substantial evidence or substantial clinical experience.
LUTALYSE® (dinoprost tromethamine) Sterile Solution, cloprostenol and other prostaglandins have been researched in hundreds of published studies. From time to time, any one particular trial may show one prostaglandin product is numerically superior to the other by chance. These differences may even be significant in some cases. Most times, the very same data do not indicate a statistical difference between the two products, just a numerical difference that it is unduly interpreted as relevant. FDA addressed these superiority claims and determined them to be unsubstantiated.

The data in the scientific literature overwhelmingly indicate there are no differences in efficacy between LUTALYSE and cloprostenol. The objective of this technical bulletin is to provide a review of the science and peer-reviewed, published data on LUTALYSE and the other prostaglandins.

**Chemical Structures**

LUTALYSE contains the naturally occurring prostaglandin F$_2$$_α$ (PGF$_2$$_α$, dinoprost) as a tromethamine salt. Its chemical structure is depicted in Figure 2. Each milliliter of LUTALYSE contains dinoprost tromethamine equivalent to 5 mg of dinoprost. Dose titration studies have indicated 25 mg of dinoprost (i.e., 5 mL of LUTALYSE) is the most appropriate dose.

The route of administration is intramuscular, whereas the intravenous administration of LUTALYSE is contraindicated. The subcutaneous route has not been fully examined; it is not an approved route of administration and, therefore, is not recommended.

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.

In the U.S., cloprostenol is sold as Estrumate® and the generic product called estroPLAN®, which contains cloprostenol sodium, a salt form of the synthetic analogue. The original chemical structure of PGF$_2$$_α$ (Figure 2) was modified to result in cloprostenol. Each milliliter of Estrumate contains 250 mcg of cloprostenol equivalent. The suggested dose of Estrumate is 2 mL, to be used intramuscularly.

Due to these structural modifications, cloprostenol has some different properties when compared with dinoprost. Cloprostenol does have a higher affinity for the PGF$_2$$_α$ receptor, and there are indications it may have a slightly longer half-life. However, as indicated below, these attributes do not correlate with a higher efficacy to synchronize estrus in cattle.

Also noteworthy is the fact that cloprostenol, as it relates to its optical orientation, is a racemic solution. That means it can be either dextrorotatory (D-) or levorotatory (L-). It was observed that only D-cloprostenol binds to the prostaglandin receptors. In some countries, companies started producing the D- form and selling the concept that this is the reason why “now” cloprostenol works better than dinoprost. Unless recent modifications were introduced, Estrumate remains a racemic solution.

**Figure 1** – Number of original research articles since 1994 published in the *Journal of Animal Science, Journal of Dairy Science* and *Theriogenology* that reported use of prostaglandins. LUTALYSE was the prostaglandin product cited in 87% (186/214) of the references.

**Figure 2** – Chemical structures of PGF$_2$$_α$ (dinoprost) and cloprostenol sodium.
The Luteolytic Process

The complete regression of the CL is the main objective to be achieved after an injection of PGF$_{2\alpha}$ or its analogues. The regression of the CL and the consequent decrease in progesterone concentration allow for the final maturation of the pre-ovulatory follicle and for an increase in the circulating levels of estradiol.

The rise in estradiol concentrations stimulate the immune system in the uterus and leads to a surge of luteinizing hormone (LH) release that will induce ovulation. These events ultimately are responsible for the main indications of prostaglandins:

- Synchronization of estrus in cattle
- Treatment of uterine infections such as pyometra
- Induction of abortion in pregnant cattle

The series of illustrations to the right demonstrate the events that occur in the reproductive tract following an injection of PGF$_{2\alpha}$ or its analogues.

As described in Figures 3A-3D, the initial injection of PGF$_{2\alpha}$ simply triggers the events that ultimately will lead to the regression of the CL and to the decrease of progesterone concentrations.

Effects on Progesterone Concentration

The decrease in progesterone concentration is the signal for the increase in estradiol, which will induce estrous behavior. Thus, when comparing the efficacy of LUTALYSE® (dinoprost tromethamine) Sterile Solution and cloprostenol, researchers measured the ability of each prostaglandin to decrease progesterone concentrations.

Seguin, et al. (1985), injected nonlactating dairy cows with either LUTALYSE (n=62) or cloprostenol (n=62) and measured plasma progesterone concentrations at 0, 2, 4, 8, 12, 24 and 48 hours after treatments (see Table 1, Page 4). In a recent study in lactating dairy cows (n=1264, Experiment 1; n=427, Experiment 2), Stevenson, et al. (2010), measured progesterone in cows receiving either LUTALYSE or cloprostenol and measured progesterone concentrations at 0, 48 and 72 hours after treatment.

In Experiment 1, LUTALYSE increased luteal regression, based on blood progesterone concentrations, from 86.6 percent to 91.3 percent ($P<0.05$) compared with cloprostenol.

![Figure 3A](image)

- This depicts the reproductive tract with the uterine body, uterine horns, oviducts, and right and left ovaries are in blue. A corpus luteum (CL; in orange) is depicted on the right ovary, and a dominant follicle is shown (in red) on the left ovary. The CL in the right ovary is actively producing progesterone. Secretion of estradiol by the dominant follicle is low, due to the high concentrations of progesterone secreted by the CL.

![Figure 3B](image)

- The events that follow an injection of PGF$_{2\alpha}$: the injected PGF$_{2\alpha}$ reaches the CL (1) and functions as a “trigger” that induces the secretion of oxytocin from the CL (2). Oxytocin secreted by the CL reaches the uterus and stimulates the release of endogenous PGF$_{2\alpha}$ (3). The endogenous PGF$_{2\alpha}$ goes back to the CL and induces the release of more oxytocin.

![Figure 3C](image)

- The continuous PGF$_{2\alpha}$-oxytocin cycle is triggered by the initial injection of PGF$_{2\alpha}$. The oxytocin produced by the CL continues to stimulate the secretion of endogenous PGF$_{2\alpha}$ by the uterus, which further stimulates the secretion of oxytocin by the CL in a classic feedback mechanism. As the CL regresses, concentrations of progesterone decrease. This cycle continues until the CL is completely regressed.

![Figure 3D](image)

- In Figure 2D, at the end of the feedback cycle, the CL is completely regressed and, in its place, there only remains a scar (corpus albicans). Since progesterone is not being produced, secretion of estradiol from the dominant follicle is increased. Estradiol will reach behavioral centers in the brain and stimulate estrous behavior. Estradiol will also induce a surge of luteinizing hormone (LH) that leads to ovulation.
In Experiment 2, LUTALYSE® (dinoprost tromethamine) Sterile Solution increased luteal regression from 69.1 percent to 75.8 percent ($P<0.05$) compared with cloprostenol in cows with one or more CL, regardless of the number of CL present (Table 2).

Data in Table 1 indicate there is no difference in the rate of progesterone decline after treatments with either LUTALYSE or cloprostenol. In his 1984 study, Johnson also reported no differences in the decline of milk progesterone concentrations at 48 hours following injections of LUTALYSE or cloprostenol in lactating dairy cows. However, Stevenson, et al. (2010), reported that a higher ($P<0.01$) proportion of cows with blood progesterone concentrations ≥1 ng/mL prior to treatment had low (<1 ng/mL) blood progesterone 72 hours after treatment when treated with LUTALYSE compared with cloprostenol.

In a 1988 study, Guay, et al., measured both serum progesterone and estradiol concentrations at 0 and 24 hours after LUTALYSE or cloprostenol treatment in Holstein heifers that had been submitted to a superovulation treatment. Results (Table 3) also indicate there is no difference in the ability of LUTALYSE and cloprostenol to induce CL regression.

Concentration of estradiol — which induces onset of estrous behavior — also did not differ between treatments. Thus, there is no defensible physiological reason for the intensity or duration of estrous behavior to differ following injections of LUTALYSE or cloprostenol.

### Table 1 — Plasma progesterone concentrations at various intervals after administration of LUTALYSE (n=62) or cloprostenol (n=62) in nonlactating dairy cows.

<table>
<thead>
<tr>
<th>Hours after treatment</th>
<th>LUTALYSE Mean (ng/ml)</th>
<th>% (as of 0 h)</th>
<th>Cloprostenol Mean (ng/ml)</th>
<th>% (as of 0 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.34</td>
<td>100</td>
<td>3.21</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>1.54</td>
<td>46</td>
<td>1.56</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>1.36</td>
<td>41</td>
<td>1.37</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>1.05</td>
<td>31</td>
<td>0.99</td>
<td>31</td>
</tr>
<tr>
<td>12</td>
<td>0.45</td>
<td>13</td>
<td>0.36</td>
<td>11</td>
</tr>
<tr>
<td>24</td>
<td>ND*</td>
<td>—</td>
<td>ND</td>
<td>—</td>
</tr>
<tr>
<td>48</td>
<td>ND</td>
<td>—</td>
<td>ND</td>
<td>—</td>
</tr>
</tbody>
</table>

*ND = values below assay detection limits.

### Table 2 — Proportion of cows undergoing luteal regression by 72 hours after treatment and percent pregnant following AI in cows treated with Lutalyse or cloprostenol as part of a timed-AI protocol.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Herds (n)</th>
<th>N</th>
<th>Luteal regression</th>
<th>Pregnancy rate</th>
<th>Cloprostenol</th>
<th>P</th>
<th>LUTALYSE</th>
<th>Cloprostenol</th>
<th>P</th>
<th>LUTALYSE</th>
<th>Cloprostenol</th>
<th>P</th>
<th>LUTALYSE</th>
<th>Cloprostenol</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevenson, et al., 2010</td>
<td>6</td>
<td>1,264</td>
<td>91.3</td>
<td>90.6</td>
<td>P&lt;0.05</td>
<td>37.8</td>
<td>36.7</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experiment 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevenson, et al., 2010</td>
<td>1</td>
<td>427</td>
<td>78.5</td>
<td>69.1</td>
<td>P&lt;0.05</td>
<td>32.8</td>
<td>31.3</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experiment 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 — Serum progesterone and estradiol-17β concentrations (mean ± SEM) for superovulated Holstein heifers (n=150) treated with LUTALYSE® (dinoprost tromethamine) Sterile Solution or cloprostenol.

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Time (hours)</th>
<th>LUTALYSE Mean (ng/ml)</th>
<th>Cloprostenol Mean (ng/ml)</th>
<th>P</th>
<th>LUTALYSE Mean (ng/ml)</th>
<th>Cloprostenol Mean (ng/ml)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone (ng/ml)</td>
<td>0</td>
<td>8.0 ± 0.4</td>
<td>6.9 ± 0.4</td>
<td>NS*</td>
<td>45.8</td>
<td>20.8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>NS</td>
<td>60.0</td>
<td>64.3</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol-17β (pg/ml)</td>
<td>0</td>
<td>26.6 ± 2.2</td>
<td>23.2 ± 1.3</td>
<td>NS</td>
<td>51.2</td>
<td>50.6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>44.9 ± 3.5</td>
<td>46.8 ± 2.8</td>
<td>NS</td>
<td>65.5</td>
<td>67.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS = differences were not significant.

### Table 4 — Reported estrus detection, conception rates and pregnancy rates of studies published in the scientific literature that compared the efficacy of LUTALYSE and cloprostenol to synchronize estrus in cattle.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type†</th>
<th>N†</th>
<th>Estrus detection rate‡ (%)</th>
<th>Conception rate‡ (%)</th>
<th>Pregnancy rate‡ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LUTALYSE</td>
<td>Cloprostenol</td>
<td>P</td>
</tr>
<tr>
<td>Johnson, 1984</td>
<td>LDC</td>
<td>52</td>
<td>61.5</td>
<td>42.3</td>
<td>NS*</td>
</tr>
<tr>
<td>Seguin, et al., 1985</td>
<td>NLDC</td>
<td>124</td>
<td>88.7</td>
<td>96.8</td>
<td>NS</td>
</tr>
<tr>
<td>Turner, et al., 1987</td>
<td>LDC</td>
<td>245</td>
<td>66.1</td>
<td>65.3</td>
<td>NS</td>
</tr>
<tr>
<td>Saloverson, et al., 2002</td>
<td>BH</td>
<td>1002</td>
<td>85.9</td>
<td>88.7</td>
<td>NS</td>
</tr>
<tr>
<td>Martineau, 2003</td>
<td>LDC-DH†</td>
<td>203</td>
<td>85.9</td>
<td>82.8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>404</td>
<td>82.6</td>
<td>83.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

1 Percentage of animals detected in estrus relative to the total number of animals within each group.  
2 Percentage of animals that conceived relative to the number of animals inseminated.  
3 Percentage of animals that conceived relative to the total number of animals within each group.  
4 Type of cattle used in the study (LDC=lactating dairy cows; NLDC=nonlactating dairy cows; 
   BC=beef cows; BH=beef heifers; DH=daity heifers).  
5 Number of animals included in the experiment.  
6 NS = differences were not statistically significant.  
7 Includes only cows injected with LUTALYSE and cloprostenol intramuscularly.  
8 Includes both intramuscular and intravenous route of administration for LUTALYSE and cloprostenol.
Fertility of Cattle Treated with LUTALYSE or Cloprostenol

Peer-reviewed studies that compared the efficacy of LUTALYSE® with cloprostenol to synchronize estrus in cattle are summarized in Table 4 (on page 4).

Results from every study and the overall interpretation from the collective data point to the same conclusion: There are no differences in the efficacy between LUTALYSE® (dinoprost tromethamine) Sterile Solution and cloprostenol to synchronize estrus in cattle.

LUTALYSE and Cloprostenol Effects on Synchrony of Estrus

There are no differences in the tightness of estrous synchronization following injections of LUTALYSE or cloprostenol. This was the common interpretation of data reported by research groups that compared both products (see Figure 4).

Data depicted in Figure 4 indicate the lack of difference in efficacy of LUTALYSE and cloprostenol to induce estrus in beef heifers according to the 2002 study by Salverson, et al. This is an important observation because this was a multilocation study (n=5) that included a relatively large number of heifers (n=1002). Authors concluded that LUTALYSE and cloprostenol were equally efficacious for synchronous induction of a fertile estrus.

Similarly, in nonlactating Holstein cows, in the 1985 study by Seguin, et al., and in Angus cows and heifers in the 1987 study by Turner, et al., researchers did not observe any differences in tightness of estrous synchronization between LUTALYSE and cloprostenol. The interval from prostaglandin treatment to estrus during superovulation treatments of dairy heifers did not differ between LUTALYSE (50.46 + 2.3 hours) and cloprostenol (45.33 + 1.65 hours) according to the 1990 study by Desaulniers, et al. The latter research group also did not observe differences in the interval from treatment with LUTALYSE or cloprostenol treatment to estrus (7.4 + 0.34 day and 7.58 + 0.35 day, respectively) in previously superovulated heifers that had multiple corpora lutea. Suggestions that cloprostenol induces a tighter synchronized estrus or that cloprostenol-treated cattle exhibit estrous behavior quicker than when injected with LUTALYSE are inaccurate.

Frequently Asked Questions on the Effects of LUTALYSE Versus Cloprostenol

Because the overall interpretation of published data is that LUTALYSE® (dinoprostone tromethamine) Sterile Suspension and cloprostenol have the same level of efficacy to synchronize estrus in cattle, questions have been raised about differences under very specific circumstances. Some of those are addressed below.

1. Does cloprostenol induce a “stronger” heat than LUTALYSE?

There is no physiological reason for such an effect. Prostaglandins do not induce estrus directly as discussed above. Rather, prostaglandins induce estrus by inducing luteolysis and decreasing progesterone concentrations in the blood. The reduction in progesterone concentrations allows the pre-ovulatory follicle to increase its production of estradiol, which will induce estrous behavior. As indicated above in the 1988 study, Guay, et al., reported no differences in estradiol concentrations at 24 hours after injections of LUTALYSE or cloprostenol.

It has been reported that concentrations of estradiol at estrus are reduced in lactating dairy cows, especially cows with high milk production. This reduction of estradiol concentrations was associated with increased steroid metabolism in the liver, resulting in dairy cows expressing estrus with less intensity and duration. Such an
observation has not been reported in dairy heifers or in beef cattle. This situation in dairy cows is not associated with the efficacy of LUTALYSE® (dinoprost tromethamine) Sterile Solution, cloprostenol or any other prostaglandin product. Suggestions that switching from LUTALYSE to cloprostenol would correct the current situation in dairy cows because cloprostenol induces a “stronger” heat are unsubstantiated.

In addition, messages suggesting Estrumate produces a stronger heat because of prolonged half-life are unsubstantiated. This conclusion was drawn from research conducted in swine. Estrumate is approved for use in cattle only and thus any conclusions drawn from research in other species are irrelevant. FDA called use of these half-life values as not relevant and serving only to exaggerate the differences between Estrumate and LUTALYSE.

2. Does the dose of LUTALYSE need to be increased for large-framed cattle?

Questions regarding dose or opinions that a higher dose is necessary are typically associated with poor results in reproductive performance without an apparent explanation. Frustrated producers and veterinarians may be inclined to shift the blame to product efficacy. Despite this, there are no conclusive data that support the recommendation for a higher dose of LUTALYSE in large-framed cattle. A recent study by Stevenson, et al. (2010), reinforced this conclusion. Rates of luteolysis or pregnancy in 1,264 lactating dairy cows from multiple dairy operations were evaluated after either LUTALYSE or cloprostenol was injected as part of a timed-insemination program. This study reported that LUTALYSE increased ($P < 0.05$) the proportion of cows with luteal regression compared with cloprostenol. The percent of cows pregnant after the first artificial insemination (AI) service was not different.

Dose titration studies conducted in both heifers and adult cows have indicated the label dose (25 mg; 5 mL) is the most effective one. In the 1985 study, Seguin, et al., categorized cows according to weight (from less than 1,000 pounds to more than 1,500 pounds) and concluded there was no evidence that larger cows had more response problems or that there were differences in efficacy of LUTALYSE and cloprostenol according to cow weight.

One 2003 study in Europe by Répási, et al., compared the efficacy of the label dose of dinoprost (25 mg; n=20) versus a higher dose (35 mg; n=19) in adult lactating dairy cows. Cows were more than 40 days postpartum and were diagnosed to have a CL by ultrasound. Researchers detected no significant differences between the two doses, their effects on CL regression (area of luteal tissue measured by ultrasound) or on rate of decrease of progesterone concentrations. Differences between the 25 mg and the 35 mg dose also were not observed in estrous-detection rates (95 percent and 84.2 percent, respectively) and conception rates (31.6 percent and 31.2 percent, respectively).

3. Do I need to inject a higher dose of LUTALYSE® (dinoprost tromethamine) Sterile Solution in timed-artificial-insemination (AI) programs?

It was observed that between 5 percent and 19 percent of cattle submitted to timed-AI programs such as Ovsynch® may fail to regress their CL following injection of prostaglandins. Such failure was associated with reduced pregnancy rates to timed insemination. Because the initial injection to induce an LH surge in an Ovsynch program causes more cows to have two corpora lutea when they receive prostaglandin treatment seven days later, researchers initially believed there might be a need to increase the dose of LUTALYSE to reduce the frequency of CL regression failures.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>Pregnancy rates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUTALYSE</td>
<td>297</td>
<td>36%</td>
</tr>
<tr>
<td>Cloprostenol</td>
<td>297</td>
<td>41%</td>
</tr>
<tr>
<td>LUTALYSE (split-dose)</td>
<td>275</td>
<td>39%</td>
</tr>
</tbody>
</table>

*No differences in pregnancy rates were observed.
Although studies with higher doses of LUTALYSE were conducted, no trials directly compared the efficacy of label versus higher doses on timed-insemination success. Comparisons of results from different studies are not appropriate due to the many other factors that impact product performance. However, the use of higher doses of LUTALYSE did not seem to induce significant increases in pregnancy rates to timed insemination. As a result, the same research groups that initially started using higher doses of LUTALYSE chose to use the label-recommended dose in more recent studies.

Most likely, the use of higher doses of LUTALYSE — or cloprostenol — in timed-insemination programs either does not result in increased pregnancy rates or the magnitude of the benefit is so small it would be too difficult to detect. Thus, the current recommendation is the label dose of LUTALYSE (25 mg) is the most appropriate for timed-AI programs. Furthermore, Stevenson, et al. (2010), showed LUTALYSE administered at the label dose is effective in inducing CL regression when used in timed-AI protocols across multiple dairy operations, and the proportion of cows pregnant following first AI was not different for LUTALYSE versus cloprostenol.

4. Which product works better for timed-AI programs?

For the reasons cited in the answer above, failure of complete CL regression was judged to be associated with reduced efficacy of LUTALYSE. These opinions indicated either the dose of LUTALYSE® (dinoprost tromethamine) Sterile Solution needed to be increased or cloprostenol was more effective in timed-AI programs.

This specific question was addressed by the 2003 study by Hiers, et al. Nonlactating beef cows (mostly Bos indicus x Bos taurus) were treated with the CoSynch program with concurrent heat suppression. All cows received an injection to induce an LH surge on Day 0, then heat was suppressed on Days 1 to 7, and at Day 7 cows received either an injection of LUTALYSE, an injection of cloprostenol or a half-dose of LUTALYSE at Day 7 and another half-dose at Day 8 (split-dose). All cows received a second injection to induce an LH surge and were timed-inseminated at Day 9 (approximately 72 to 80 hours after heat suppression). Results are depicted in Table 5. No differences in pregnancy rates were observed for the treatment groups. This is in agreement with work by Stevenson, et al. (2010), who showed the proportion of cows pregnant following timed AI across multiple herds was not different for LUTALYSE versus cloprostenol.

5. Does cloprostenol work better than LUTALYSE in Bos indicus cattle?

Data do not support any claims of improved performance of cloprostenol in Bos indicus cattle. There is some evidence that Bos indicus breeds and their crosses are more refractory to prostaglandin treatments in general. Cows close to Days 5 and 6 of the estrous cycle are said to be a greater problem for Bos indicus. The opinion is cloprostenol would be more effective at that specific stage of the cycle. The data above in the 2003 study by Hiers, et al., indicated no differences in efficacy between LUTALYSE and cloprostenol in Bos indicus crosses. Authors went further and indicated that in a preliminary study with Bos indicus crosses, results suggested there were no differences in the ability to induce luteolysis as measured by the decrease in progesterone concentrations after injections of LUTALYSE or cloprostenol. Once more, there is no indication that cloprostenol would have greater efficacy than LUTALYSE.
If efficacy is the same, why choose LUTALYSE?

Efficacy is not the only consideration in product choice among producers and veterinarians. It is important to recognize the benefits to using LUTALYSE® (dinoprost tromethamine) Sterile Solution extend beyond the product itself. Consider below the reasons that LUTALYSE is the undisputable market leader:

1) **Product support:** Pfizer Animal Health provides expertise on capturing the most value from a dairy producer’s investment. The team of technical experts supporting Pfizer Animal Health products work with customers and their veterinarians to effectively incorporate each solution into the dairy’s reproductive protocols. This ensures producers are protecting reproductive efficiency and capturing an effective return on investment. And more important, this ensures the reproductive program is designed to get cows bred and protect the growing fetus from reproductive disease.

2) **Research backing:** LUTALYSE is the most researched and studied prostaglandin in the marketplace. A review of scientific publications conducted in the U.S. in the past 10 years clearly shows the depth of research of LUTALYSE as compared with other brands. The vast majority of those scientific studies were conducted with Pfizer Animal Health support, demonstrating the company’s commitment to the understanding of all aspects of the biology and practical use of LUTALYSE under commercial conditions.

What does that mean to customers? That means through research and practical experience, Pfizer Animal Health personnel know better than any of our competitors how to make LUTALYSE work for our customers’ operations. This means we have the answers producers and veterinarians are looking for, and those answers are rooted in solid scientific data. Pfizer Animal Health is committed to support research and will continue to provide the most current information to customers.

3) **Reproductive solution:** Prostaglandins are an integral part of any reproductive program, but there is more to reproductive programs than prostaglandins. Backed by years of proven success, Pfizer Animal Health products are the leading choice of dairy producers across the country and can help improve the efficiency of a reproductive program. In addition to LUTALYSE, Pfizer Animal Health has a complete line of reproductive solutions, including FACTREL® (gonadorelin hydrochloride) Sterile Solution and Eazi-Breed™ CIDR® Cattle Insert. LUTALYSE is the only prostaglandin product approved for use in synchronization protocols with Eazi-Breed CIDR Cattle Insert. A synchronization program, including leading products from Pfizer Animal Health, can improve the efficiency and success of breeding programs.

**Conclusion**

Data in the scientific literature conclusively indicate there is no difference in efficacy or product performance between LUTALYSE and cloprostenol. As discussed, there are a large number of peer-reviewed, published articles by many respected researchers that continue to demonstrate this point, with research published as recently as 2010. Other messages indicating differently are a misinterpretation of the science. FDA has shown it will not tolerate any misinterpretation or misuse of science to draw unsubstantiated conclusions.

Ultimately, the backbone of a successful reproduction program is much broader than just the prostaglandin used. Pfizer Animal Health technical experts are among the most respected in the dairy industry and are consistently sought-after speakers. When choosing products from Pfizer Animal Health, producers are not only choosing innovative and market-leading formulas but also our commitment to providing solutions necessary for a dairy operation to survive.

Pfizer Animal Health is committed to providing veterinarians with products that carry the most robust label claims that science can validate. Our promise is that science will validate every claim for every one of our products. We are committed to continued research on the physiological activity of LUTALYSE as well as supporting ongoing scientific research that veterinarians and producers need to make appropriate decisions about the use of prostaglandins in their herds. As we learn more about the science behind LUTALYSE® (dinoprost tromethamine) Sterile Solution, we will continue to pursue new approved label indications for its use.
References


Mares treated with either 400 mg or 800 mg exhibited more profound symptoms. The excessive hyperstimulation of Mares did not appear to sustain adverse effects following termination of the side effects and to a lesser extent, the 200 mg dose groups were transient in nature, lasting for a few minutes to several hours.

Prostaglandins, especially PGF2\alpha, have been shown to 1) increase in the uterus and blood to levels similar to levels achieved by exogenous administration which elicited luteolysis, 2) be capable of crossing from the uterine vein to the overlying ovarian vein and to the ovarian artery (ovarian (cephalic), and 4) capable of causing the release of prostaglandins from the ovary. Data suggest prostaglandins, especially PGF2\alpha and PGE2, may be involved in the process of ozone-induced ovulation and are believed to cause increase in blood pressure, bronchoconstriction, and smooth muscle stimulation in certain tissues.

SAFETY AND TOXICITY
Luteolytically, dinoprost was non teratogenic in rats when administered only at 1,25, 3.0, 10.0, and 20.0 mg/kg/day from day 6th-15th of gestation or when administered subcutaneously at 0.1, 0.5, and 1.0 mg/kg/day on gestation days 7, 8, 9 and 20. In horses given a single intravaginal implant at 5 mg, the uterus and myometrium were affected. These effects were dose-related as all horses treated with 5 mg or more displayed signs of estrus on days 1-3 post implantation, one horse had bloody vaginal discharge on day 4, and the remaining 7 horses died following injection with 5 mg or more of dinoprost. All 7 horses died within 15 minutes of injection and survived less than 1 hour after injection with 25 mg dinoprost, but had not reached baseline at 24 hours after injection. No dose-related group effect was seen in horses treated with 5 mg of dinoprost. All horses treated with at least 10X the injection dose (25 mg) for 5 mg demonstrated no signs of estrus.

In one study, no significant effect on the estrous cycle was observed when 0.25, 0.5, 1.0, 2.0, 5.0, 10.0, and 20.0 mg/kg of PGF2\alpha was given by subcutaneous, intramuscular, or intravenous routes. Although no significant adverse effects associated with 0.25 mg/kg dose were observed, it was noted that estrus was not induced in any of the animals. The results indicated no treatment-related effects from dinoprost treatment that were deleterious to the health of the animals or to their offspring.

Pigs: PGF2 alpha Tham in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during estrus was separated from blood cells and the concentration of PGF2 alpha was determined using the chromogenic assay for PGF2 alpha. The results were as follows:

- For Intramuscular Use for Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers, LUTALYSE is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum.
- For Intramuscular Use for Estrus Synchronization in Bovine Blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 3H PGF2 alpha in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equimolar doses of PGF2 alpha, and in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during estrus was separated from blood cells and the concentration of PGF2 alpha was determined using the chromogenic assay for PGF2 alpha. The results were as follows:

- For Intramuscular Use for Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers, LUTALYSE is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum.
- For Intramuscular Use for Estrus Synchronization in Bovine Blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 3H PGF2 alpha in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equimolar doses of PGF2 alpha, and in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during estrus was separated from blood cells and the concentration of PGF2 alpha was determined using the chromogenic assay for PGF2 alpha. The results were as follows:

- For Intramuscular Use for Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers, LUTALYSE is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum.
- For Intramuscular Use for Estrus Synchronization in Bovine Blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 3H PGF2 alpha in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equimolar doses of PGF2 alpha, and in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during estrus was separated from blood cells and the concentration of PGF2 alpha was determined using the chromogenic assay for PGF2 alpha. The results were as follows:

- For Intramuscular Use for Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers, LUTALYSE is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum.
- For Intramuscular Use for Estrus Synchronization in Bovine Blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 3H PGF2 alpha in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equimolar doses of PGF2 alpha, and in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during estrus was separated from blood cells and the concentration of PGF2 alpha was determined using the chromogenic assay for PGF2 alpha. The results were as follows:

- For Intramuscular Use for Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers, LUTALYSE is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum.
- For Intramuscular Use for Estrus Synchronization in Bovine Blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 3H PGF2 alpha in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equimolar doses of PGF2 alpha, and in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during estrus was separated from blood cells and the concentration of PGF2 alpha was determined using the chromogenic assay for PGF2 alpha. The results were as follows:

- For Intramuscular Use for Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers, LUTALYSE is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum.
Factrel®
GONADORELIN HYDROCHLORIDE

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
FACTREL (gonadorelin hydrochloride) is a sterile solution containing 50 micrograms of synthetic gonadorelin (as hydrochloride) per mL in aqueous formulation containing 0.6% sodium chloride and 2% benzyl alcohol (as a preservative). Gonadorelin is the gonadotropin releasing hormone (GnRH) which is produced by the hypothalamus and causes the release of the gonadotropin luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. FACTREL (gonadorelin hydrochloride) has the identical amino acid sequence as endogenous gonadorelin; 5-oxo Pro-His-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂ with identical physiological activities. The molecular weight of gonadorelin is 1182 with a molecular formula of C₅₅H₇₅N₁₇O₁₃. The corresponding values for gonadorelin hydrochloride are 1219 (1 HCl) expressed as C₅₅H₇₅N₁₇O₁₃HCl, or 1255 (2 HCl) expressed as C₅₅H₇₅N₁₇O₁₃H₂Cl.

MECHANISM OF ACTION
Follicular cysts are enlarged non-ovulatory follicles resulting from a malfunction of the neuroendocrine mechanism controlling follicular maturation and ovulation. Exogenous administration of agents possessing luteinizing hormone (LH) activity, such as pituitary extracts or human chorionic gonadotropin, often causes ovulation or regression of follicular cysts. FACTREL induces release of endogenous luteinizing hormone (LH) to produce this same effect. No significant differences have been demonstrated in days from treatment to conception, frequency of cows conceiving at first or subsequent heats, or conception rates among treated or non-treated control animals.

INDICATIONS
FACTREL (gonadorelin hydrochloride) is indicated for the treatment of ovarian follicular cysts in cattle. The treatment effect of FACTREL when used in cattle with ovarian follicular cysts is a reduction in the number of days to first estrus.

DOSEAGE
The recommended dosage of FACTREL is 100 mcg/cow intramuscularly.

RESIDUE WARNING
Because FACTREL is identical to endogenous GnRH such that both are rapidly metabolized without detectable levels in milk or tissue, no withdrawal period is required.

STORAGE CONDITIONS
Store at refrigerator temperature 2° to 8°C (36° to 46°F).

SAFETY AND TOXICITY
In cows the intramuscular administration of up to 25 times recommended dosage (2,500 mcg/day) of FACTREL for 3 days did not affect any physiological or clinical parameter. Likewise, single intramuscular doses of 5 times recommended dosage (500 mcg) did not interfere with pregnancy. No evidence of irritation at injection site was found in any animal.

HOW SUPPLIED
FACTREL (gonadorelin hydrochloride) solution 50 mcg/mL is available in 20 mL multidose vials (box of one). NDC 0856-4311-02 – 20 mL – box of 1

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

01203 Rev. Apr. 2003 4310H