Using Estradiol Cypionate (ECP®) vs. GnRH in Controlled A.I.-Breeding Programs
Why Substitute Estrogen for GnRH?

- Estrogen induces:
  - Sexual behavior—estrus
  - Uterine tone
  - Secretion of mucus

- Cows may be somewhat easier to inseminate at timed AI.

- Increased estrus activity has positive psychological effects on those inseminating cows.

- Estrogen is significantly less costly.
How Do Estrogen and GnRH Work?

**GnRH** is secreted by the hypothalamus and induces release of LH and FSH from the AP.

GnRH induces the LH surge in response to increased estrogen (E) associated with the onset of estrus.

LH

Onset of estrus

Estrus

27 hr

Onset of ovulation

Hypothalamus

Anterior pituitary gland (AP)

GnRH

Follicle

27 hr
Estrogens

**Estradiol-17β**
- Principal estrogen secreted by the follicle

**Estradiol benzoate**
- Mimicks estradiol-17β most closely (half-life nearly equal)

**Estradiol cypionate**
- Longer-acting estrogen (sold as ECP®)

**Estradiol valerate**
- Longest-acting estrogen; was part of Syncro-Mate B® estrus-synchronization protocol (not available)
Extra Label Use of Drugs

• Extra label use means a drug is used for purposes NOT listed as one of its Indications on the bottle label or bottle insert.

• For example, the label for each GnRH product indicates that its approved use is for the treatment of ovarian follicular cysts.

• Use of GnRH in any estrus-synchronization or ovulation control program is considered to be an extra label use.
Extra Label Use of Drugs

• GnRH products have therapeutic approvals for use in cattle in the U.S.

• Strict interpretation of Animal Medicinal Drug Use Clarification Act (AMDUCA) is that GnRH products cannot be used for production purposes in cattle.

• However, GnRH products are being used extensively for estrus-synchronization programs by veterinarians and academic researchers who have published their results in scientific journals and producer press.
Extra Label Use of Drugs

• GnRH is a peptide (very small protein with a short blood half life) with no known health concerns.

• FDA must have minimal concerns regarding use of GnRH products in estrus-synchronization programs because no known prosecutions have been initiated.
Illegal Use of Drugs and Compounding of Products

- Estradiol benzoate (EB) has no human or animal approval in the U.S.
- Strict interpretation of AMDUCA is that EB cannot be used for production purposes in cattle.
- Therefore, use of EB in cattle for estrus-synchronization programs is illegal.
- Use of EB also is illegal when compounded with any other approved product.
- Use of the Eazi-Breed™ CIDR® Cattle insert plus Lutalyse® is an approved compounding of products.
What Estrogen is Approved?

- Estradiol cypionate (ECP) has a therapeutic label for use in cattle in the U.S.
- It is the only estrogen approved for use in cattle is ECP® (Pharmacia)
- ECP has multiple label indications including “to correct anestrus [absence of heat period] in the absence of follicular cysts” at 3 to 5 mg doses.
Use of ECP in Breeding Programs

- Strict interpretation of AMDUCA is that ECP cannot be used for production purposes in cattle.
- Because ECP is an estrogen, it is of concern to the U.S. Food and Drug Administration-Center for Veterinary Medicine relative to human health and safety.
Use of ECP in Breeding Programs

- ECP is being used extensively for estrus-synchronization programs by veterinarians and academic researchers who have published their results in scientific journals and producer press.
- FDA has not initiated prosecutions of either researchers or veterinarians using ECP in cattle estrus-synchronization programs.
Follicle Control

Ovulation or follicle turnover?

-7

Upfront GnRH

Synchronized initiation of a new follicular wave

0

Onset of the breeding season

PGF

GnRH

Ovulation

Upfront Estrogen

Ovulation of a smaller follicle

Ovulation of a
What Must Estrogen Do To Replace GnRH in Breeding Programs?

• Estrogen must induce upfront follicle turnover in a synchronization program in cycling cows.
• Estrogen must induce upfront ovulation in anestrous cows.
• Estrogen must induce ovulation after PGF.

• Estrogen must **not** produce “hyper-estrus” activity to prevent injury of cows caused by excessive riding and standing behavior.
• Estrogen must be easy to administer.
Upfront Follicular Control?: Cycling

- Upfront EB (1 vs. 2 mg) at CIDR-7 insertion was effective for lactating cycling cows (Day et al., 2000).

- Upfront EB vs. GnRH at PRID-8 insertion was effective in cycling replacement heifers (Lane et al., 2001).
Upfront Follicular Control?: Anestrus

- Use of EB at 0.5 or 1.0 mg dose at the time of CIDR insertion did not induce ovulation effectively in seasonally anestrous dairy cattle (Verkerk et al., 1998). Beef cattle?

- EB + CIDR reduced formation of persistent follicles in lactating anestrous dairy cows, but delayed follicular development in some anestrous cows (Rhodes et al., 2002). Beef cattle?

- Immature dominant follicles in suckled anestrous cows were less likely to ovulate after EB (Burke et al., 2001).
After luteolysis, ECP induces ovulation in lactating dairy cows and in replacement heifers (Lopes et al., 2000).

<table>
<thead>
<tr>
<th>Response</th>
<th>Kansas</th>
<th>Florida</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP to LH surge, h</td>
<td>19.1 ± 2.6</td>
<td>29.0 ± 1.8</td>
</tr>
<tr>
<td>Onset of estrus after ECP, h</td>
<td>27.8 ± 3.2</td>
<td>29.0 ± 1.8</td>
</tr>
<tr>
<td>Duration of estrus, h</td>
<td>6.9 ± 0.7</td>
<td>12.5 ± 1.8</td>
</tr>
<tr>
<td>No. of standing events</td>
<td>17.1 ± 5.2</td>
<td>20.3 ± 2.8</td>
</tr>
<tr>
<td>Total standing timed, sec</td>
<td>36.3 ± 12</td>
<td>47.6 ± 7.5</td>
</tr>
<tr>
<td>Ovulation after estrus onset, h</td>
<td>29.9 ± 2.4</td>
<td>27.5 ± 1.1</td>
</tr>
<tr>
<td>Ovulation after ECP, h</td>
<td>60.0 ± 1.8</td>
<td>55.4 ± 2.7</td>
</tr>
</tbody>
</table>
Easily Administered?

- ECP is dosed at 2 mg per mL.
- A small syringe is required to deliver 1 mg of ECP i.m. in a volume of 0.5 mL (0.5 cc).
- When injecting cows, follow Beef Quality Assurance (BQA) guidelines to reduce carcass bruising and injection site lesions (i.e., use neck injection sites).
EAZI-BREED CIDR® Cattle Insert
Use of EB + CIDR

<table>
<thead>
<tr>
<th>EB dose</th>
<th>Heifers</th>
<th>Parity 1</th>
<th>Parity 2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg</td>
<td>43% (56)</td>
<td>28% (37)</td>
<td>64% (73)</td>
</tr>
<tr>
<td>1 mg</td>
<td>51% (54)</td>
<td>41% (34)</td>
<td>51% (69)</td>
</tr>
<tr>
<td>2 mg</td>
<td>48% (56)</td>
<td>32% (36)</td>
<td>63% (72)</td>
</tr>
</tbody>
</table>

Pregnancy rates

Courtesy of Les Anderson, Univ. of Kentucky
Courtesy of Joel Yelich, Univ. of Florida

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days</th>
<th>Hours</th>
<th>PR (%)</th>
<th>(No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIDR7+EB+AIE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EB+CIDR7+EB+AIE</td>
<td></td>
<td></td>
<td>39%</td>
<td>(80)</td>
</tr>
<tr>
<td>CIDR7+EB+TAI60</td>
<td></td>
<td></td>
<td>36%</td>
<td>(77)</td>
</tr>
<tr>
<td>EB+CIDR7+EB+TAI60</td>
<td></td>
<td></td>
<td>51%</td>
<td>(87)</td>
</tr>
<tr>
<td>CIDR7+TAI48</td>
<td></td>
<td></td>
<td>38%</td>
<td>(80)</td>
</tr>
<tr>
<td>EB+CIDR7+TAI48+GnRH</td>
<td></td>
<td></td>
<td>53%</td>
<td>(85)</td>
</tr>
</tbody>
</table>
Use of ECP + CIDR

When using ECP upfront, the CIDR must be in place for **9 days**

- **G+CIDR-7+G**
  - GnRH
  - PGF
  - GnRH + TAI

- **G+CIDR-7+ECP**
  - GnRH
  - PGF
  - 0.5 mg ECP
  - TAI

- **ECP+CIDR-9+ECP**
  - 1 mg ECP
  - PGF
  - 1 mg ECP
  - TAI
## Pregnancy Rates in Suckled Angus Cows

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>Parity 1</th>
<th>Parity 2+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>G + CIDR-7 + G</td>
<td>56% (45)</td>
<td>52% (63)</td>
<td>54% (108)</td>
</tr>
<tr>
<td>G + CIDR-7 + ECP</td>
<td>61% (44)</td>
<td>72% (60)</td>
<td>67% (104)</td>
</tr>
<tr>
<td>ECP + CIDR-9 + ECP</td>
<td>44% (43)</td>
<td>52% (62)</td>
<td>51% (105)</td>
</tr>
</tbody>
</table>

*TAI at 52 to 60 hr
<table>
<thead>
<tr>
<th>Treatment*</th>
<th>Herd B</th>
<th>Herd K</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>G + CIDR-7 + G</td>
<td>50% (24)</td>
<td>31% (98)</td>
<td>34% (122)</td>
</tr>
<tr>
<td>G + CIDR-7 + ECP</td>
<td>33% (25)</td>
<td>39% (99)</td>
<td>38% (124)</td>
</tr>
<tr>
<td>ECP + CIDR-9 + ECP</td>
<td>38% (26)</td>
<td>39% (109)</td>
<td>39% (135)</td>
</tr>
</tbody>
</table>

*TAI at 52 to 60 hr
## ECP vs. GnRH

<table>
<thead>
<tr>
<th>Calf removal</th>
<th>ECP</th>
<th>GnRH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>49% (94)</td>
<td>51% (97)</td>
<td>50%* (191)</td>
</tr>
<tr>
<td>No</td>
<td>51% (90)</td>
<td>38% (88)</td>
<td>44% (178)</td>
</tr>
<tr>
<td>Total</td>
<td>50%+ (184)</td>
<td>44% (185)</td>
<td>47% (369)</td>
</tr>
</tbody>
</table>

*Different (P<0.05) from no calf removal.
+Different (P<0.05) from GnRH.
• ECP is an alternative to GnRH for upfront follicle control, but may not be as effective as GnRH for anestrous cows.

• If ECP is used upfront at CIDR insertion, the CIDR must be in place for 9 days, rather than 7 days when using GnRH.

• After CIDR removal, ECP is an alternative to GnRH after luteolysis for TAI systems.

• Pregnancy rates to TAI tended to be greater in suckled cows when treated after PGF with ECP than GnRH.
Resynchronization of Estrus

- Increase opportunity for more A.I.-sired calves
- Take full advantage of previous synchrony with little additional cost
- Facilitate heat detection of first eligible heat after A.I.
Protocols for Resynchronization of Estrus

- Previously used progestin-releasing inserts or implants
- Feeding of a progestin (e.g., MGA)
- Combination progestins with estrogen injections
- Use of Ovsynch and Heatsynch
Exp. 1:
68 dairy heifers
62 beef heifers

Days after initial AI

CIDR 13 (11-15) 20
ECP
Control
ECP

CIDR
## Exp. 1. Reproductive Traits

<table>
<thead>
<tr>
<th>Item</th>
<th>Con</th>
<th>CIDR</th>
<th>CIDR + ECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of heifers</td>
<td>44</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>PR after 1(^{st}) A.I.</td>
<td>53%</td>
<td>47%</td>
<td>60%</td>
</tr>
<tr>
<td>Return 18-26 days</td>
<td>73%</td>
<td>84%</td>
<td>90%</td>
</tr>
<tr>
<td>CR of repeat A.I.</td>
<td>60%</td>
<td>33%</td>
<td>35%</td>
</tr>
<tr>
<td>26-day PR</td>
<td>72%</td>
<td>60%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Exp. 3:
588 suckled beef cows

Days after initial TAI
Exp. 2. Reproductive Traits

<table>
<thead>
<tr>
<th>Item</th>
<th>Con No. of cows</th>
<th>CIDR + EB PR after 1st A.I.</th>
<th>CIDR + ECP Return 20-23 days</th>
<th>CIDR + ECP CR of repeat A.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cows</td>
<td>292</td>
<td>151</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>PR after 1st A.I.</td>
<td>52%</td>
<td>44%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Return 20-23 days</td>
<td>29%</td>
<td>84%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>CR of repeat A.I.</td>
<td>65%</td>
<td>52%</td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>

Resynchronization of repeat estrus:

- Had no negative effect on established pregnancies.
- Increased synchrony of repeat estrus.
- Tended to reduce resynchronized conception rates after resynchronization in dairy and beef heifers.
- Produced normal conception rates at the resynchronized estrus in suckled beef cows when ECP + CIDR were used.
Thanks to the following for their financial or product support:

- **Select Sires**
- Pharmacia Animal Health
- Fort Dodge Animal Health
- Intervet
- Merial