Bovine Rhinotracheitis-Virus Diarrhea Vaccine

Indications
For vaccination of healthy cows and heifers prior to breeding for prevention of persistently infected calves caused by Bovine Virus Diarrhea (BVDV) virus types 1 and 2; as an aid in the prevention of abortion due to Infectious Bovine Rhinotracheitis (IBR) virus; for the prevention of urinary shedding of L. borrelii serovar hardjo (type hardjo-bovis); as an aid in the prevention of respiratory disease caused by IBR virus, BVDV virus types 1 and 2; and as an aid in reduction of infertility, delayed conception, or abortion caused by Campylobacter fetus var. venerealis, and leptospirosis caused by 5 serovars of Leptospira (L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae, and L. pomona).

A 12-month duration of immunity has been demonstrated against IBR-induced abortion and against disease, including persistently infected calves, caused by BVDV types 1 and 2. In addition, vaccinated animals subsequently exposed to L. borrelii serovar hardjo (type hardjo-bovis) have been shown to clear renal infections within 8 weeks of exposure.

This vaccine may be administered to pregnant cattle provided they were vaccinated, according to label directions, with any Express® FP vaccine within the past 12 months. May also be administered to calves nursing pregnant cows provided their dams were vaccinated within the past 12 months with Express FP products. See below for details.

Composition
The product in the amber glass vial contains IBR and BVDV Type 1 viruses. The plastic vial contains C. fetus and the Leptospira organisms listed above, in an adjuvant system. Contains neomycin and thimerosal as preservatives.

Directions and Dosage
Rehydrate the vaccine by adding the accompanying killed bacterin diluent to the vaccine vial. Shake well. Using aseptic technique, inject 2 mL subcutaneously or intramuscularly. If using subcutaneous route, inject in front of the shoulder and midway of the neck, away from the suprascapular lymph node. If initial vaccination, repeat with Citadel® VL5 vaccine (C. fetus-Leptospira) in 14-28 days. Calves vaccinated before 6 months of age should be revaccinated at 6 months. A 2 mL booster dose is recommended once annually.

Cows and Heifers: Using aseptic technique, annually inject a single 2 mL dose subcutaneously or intramuscularly at or about 4 weeks prior to breeding. Pregnant cows and nursing calves may be vaccinated provided they were vaccinated, according to label directions, with any Express FP vaccine within the past 12 months. See below for details. If initial vaccination, see above.

Precautions
Store out of direct sunlight at 35-45°F (2-7°C). Avoid freezing. Use entire contents when first opened. Burn containers and all unused contents. Do not vaccinate within 21 days before slaughter. Stressed cattle should not be vaccinated. Anaphylactoid reactions may occur. Antidote: Epinephrine.

Summary of BVDV Type 1 and 2 Efficacy Studies
Four non-cytopathic BVDV challenge viruses were used in five different challenge studies to determine the efficacy of this product in preventing persistently infected calves due to BVDV Types 1 and 2. The challenge viruses included two BVDV Type 1b and two BVDV Type 2 strains. The efficacy provided against challenge ranged from 91% to 100% prevention of persistent infection. The table below gives a summary of these studies.

Summary of all BVD Studies

<table>
<thead>
<tr>
<th>Challenge Virus</th>
<th>Treatment Group</th>
<th># Positive/Total</th>
<th>Total Percent Protected</th>
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</thead>
<tbody>
<tr>
<td>BVDV Type 1</td>
<td>Vaccinates</td>
<td>1 of 29</td>
<td>96%</td>
</tr>
<tr>
<td>(2 Studies)</td>
<td>Controls</td>
<td>18 of 18</td>
<td>0%</td>
</tr>
<tr>
<td>BVDV Type 2</td>
<td>Vaccinates</td>
<td>2 of 46</td>
<td>96%</td>
</tr>
<tr>
<td>(3 Studies)</td>
<td>Controls</td>
<td>29 of 29</td>
<td>0%</td>
</tr>
</tbody>
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Summary of BVD Type 1 and 2 Duration of Immunity Efficacy Studies
One hundred thirty-six seronegative heifers were enrolled in this study. Sixty-six were assigned to the BVDV Type 1 study and 70 were assigned to the BVDV Type 2 study. Thirty two animals in the BVDV Type 1 study and 35 animals in the BVDV Type 2 study were vaccinated on Day 0 with Express® FP 5-VL5. The rest of the heifers were vaccinated with Citadel® VL5. All heifers in the BVDV Type 1 study were bred on Day 285 and the heifers in the BVDV Type 2 study were bred on Day 284. Heifers in the Type 1 study were challenged with virulent BVDV Type 1b strain B) on Day 368 and the heifers in the Type 2 study were challenged on Day 374 with BVDV Type 2 strain PA 131. Temperatures, clinical observations, and blood samples were collected on multiple study days. Fetal tissues were collected on Day 440 for the Type 1 study and Day 439 for the Type 2 study. All control heifers remained seronegative to BVDV Type 1 and 2 prior to challenge.

The following table summarizes the results of the duration of immunity studies. These results indicate that a single dose of Express FP 5-VL5 administered one year prior to challenge provided fetal protection against BVDV Type 1 and 2, preventing persistently infected calves: Type 1 [prevented fraction = 0.95 (95%) with exact 95% confidence limits of (0.75,1.0)] and Type 2 [prevented fraction = 1.0 (100%) with exact 95% confidence limits of (0.83,1.0)]. Vaccination also provided protection against viremia and leukopenia: Viremia BVDV Type 1 prevented fraction = 1.0 (100%) with exact 95% confidence limits of (0.83,1.0); viremia BVDV Type 2 prevented fraction = 0.94 (94%) with exact 95% confidence limits of (0.72,1.0); leukopenia BVDV Type 1 prevented fraction = 0.60 (60%) with exact 95% confidence limits of (0.32,0.80); leukopenia BVDV Type 2 prevented fraction = 0.91 (91%) with exact 95% confidence limits of (0.58,1.0).
Challenge organism was recovered from the kidneys of 10 of 11 placebo control heifers. Negative, while 100% of the placebo-control heifers shed the challenge with Express® FP 5 -VL5. Eleven heifers were vaccinated with Express® in the study. Twenty-one heifers were vaccinated twice, 21 days apart, at weekly intervals starting at 1 week through 8 weeks post-challenge. L. borgpetersenii serovar hardjo (type hardjo-bovis) strain 203 on days BVTV Type 2

<table>
<thead>
<tr>
<th>Challenge Virus</th>
<th>Treatment Group</th>
<th>Viremia Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>BVDV Type 1</td>
<td>Vaccinates 0/22 (0%)</td>
<td>Controls 19/23 (82.6%)</td>
</tr>
<tr>
<td>BVDV Type 2</td>
<td>Vaccinates 1/18 (5.6%)</td>
<td>Controls 20/22 (90.9%)</td>
</tr>
</tbody>
</table>

Challenge Virus | Treatment Group | Leukopenia Positive |
<table>
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</thead>
<tbody>
<tr>
<td>BVDV Type 1</td>
<td>Vaccinates 8/22 (36.4%)</td>
<td>Controls 21/23 (91.3%)</td>
</tr>
<tr>
<td>BVDV Type 2</td>
<td>Vaccinates 1/18 (5.6%)</td>
<td>Controls 14/22 (63.6%)</td>
</tr>
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</table>

The proportion positive for abortion included 2/13 (15.4%) for heifers vaccinated 12 months prior to challenge for L. hardjo. Heifers vaccinated 8 months prior to challenge and 27 heifers were administered Citadel VLS for the challenge control group. Vaccinates and controls were separated 25 days post-vaccination then re-commingled. All heifers were artificially inseminated on Day 193 and a clean up bull was put in with the heifers from Day 193 to Day 207. Heifers were then challenged on Day 386 with IBR Cooper strain, IV, via jugular venipuncture. Post-challenge all heifers were commingled for the duration of the study.

The health of the calves from the enrolled cattle was monitored for 30 days after birth. There were no differences noted in the health status of calves between the two treatment groups. In addition, a separate newborn calf serology study was conducted. A total of 120 calves from dams revaccinated in the second or third trimester were negative for precolostral antibodies to Bovine Virus Diarrhea Types 1 and 2 and Infectious Bovine Rhinotracheitis, further demonstrating that the Express® MLV products do not cause fetal infection when administered during pregnancy to previously vaccinated cows or heifers.

Fetal health risks associated with vaccination of pregnant animals with modified live vaccines cannot be unequivocally determined by clinical trials conducted for licensure. Management strategies based on vaccination of pregnant animals with modified live vaccines should be discussed with a veterinarian. No vaccine can be expected to have 100% efficacy under all conditions. A small number of calves persistently infected with BVDV may have a devastating effect on herd health.

Note
It is possible that healthy-appearing cattle can be persistently infected with or incubating virulent BVD virus at the time of vaccination. In view of these findings and suggested causes, BVD vaccine is contraindicated in persistently infected cattle and use should be limited only to healthy, immunocompetent, unstressed cattle.

Caution
Animal inoculation only. Accidental injection into humans can cause serious local reactions. Contact a physician immediately if accidental injection occurs.

Summary of Pregnant Cow Safety Study
Safety in pregnant cows and heifers was demonstrated in a field study that utilized more than 1600 cattle from three separate herds, as well as a serological study from a fourth herd. All cows and heifers enrolled in the study were vaccinated prior to breeding with Express® FP 10, a modified live virus (MLV) vaccine containing Infectious Bovine Rhinotracheitis (IBR), Bovine Virus Diarrhea (BVD) Type 1, BVD Type 2, Parainfluenza 3 (PI3), and Bovine Respiratory Syncytial Virus (BRSV), as well as Leptospira canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae, L. pomona bacterin. Approximately one-third of the enrolled cattle were assigned to each one of the three trimesters. After confirmation of pregnancy status, a second vaccination was administered during the assigned trimester. Half of each trimester group was given Express® FP 10 and the remaining half was given the Lepto 5 bacterin. All of the enrolled cattle were observed closely through calving. Any fetal losses were recorded and fetuses were subjected to a full necropsy. Fetal losses were similar in both treatment groups. Overall fetal losses were 1.6% (13 of 810) in the test vaccination group and 1.9% (15 of 776) in the control group. There were no abortions or fetal losses diagnosed as due to IBR or BVD. The health of the calves from the enrolled cattle was monitored for 30 days after birth. There were no differences noted in the health status of calves between the two treatment groups.

Summary of IBR abortion Duration of Immunity Efficacy Studies
Eighty-one heifers negative with IBR titers <1:2 were enrolled in this study to evaluate the efficacy and duration of immunity of the IBR modified live vaccine component in an IBR abortion challenge model. Twenty-five heifers were administered Express FP 5-VL5 12 months prior to challenge, 29 were administered Express FP 5-VL5 8 months prior to challenge and 27 heifers were administered Citadel VLS for the challenge control group. Vaccinates and controls were separated 25 days post-vaccination then re-commingled. All heifers were artificially inseminated on Day 193 and a clean up bull was put in with the heifers from Day 193 to Day 207. Heifers were then challenged on Day 386 with IBR Cooper strain, IV, via jugular venipuncture. Post-challenge all heifers were commingled for the duration of the study.

The proportion positive for abortion included 2/13 (15.4%) for heifers vaccinated 12 months prior to challenge (p<0.0001), 5/19 (26.3%) for heifers vaccinated 8 months prior to challenge (p=0.0001) and 18/19 (94.7%) for the control group. Fetal tissues tested negative for other potential causes of abortion, which supported that post-challenge abortions were IBR-related and that abortions were prevented in heifers challenged with IBR 12 months post-vaccination (prevented fraction for abortion = 0.84 (84.0%) with exact 95% confidence limits of (0.54, 0.98).

Summary of L. borgpetersenii serovar hardjo (type hardjo-bovis) Efficacy Study
Thirty-two heifers sero-negative by MAT against L. hardjo were enrolled in the study. Twenty-one heifers were vaccinated twice, 21 days apart, with Express® FP 5-VL5. Eleven heifers were vaccinated with Express® FP 5 as the placebo. All heifers were challenged intracoelomally with L. borgpetersenii serovar hardjo (type hardjo-bovis) strain 203 on days 105, 106 and 107 post first-vaccination. Urine samples were obtained at weekly intervals starting at 1 week through 8 weeks post-challenge. The heifers were sacrificed at 8 weeks post-first challenge. Kidney samples were obtained at necropsy. Urine and kidney samples were cultured to confirm positive or negative status based on recovery of the challenge organism. All urinary culture results from vaccinated heifers were negative, while 100% of the placebo-control heifers shed the challenge organism in the urine for a minimum of 7 days post-challenge. All kidney culture results from vaccinated heifers were negative, whereas the challenge organism was recovered from the kidneys of 10 of 11 (90.9%) placebo control heifers.
Indications: For vaccination of healthy cows and heifers prior to breeding for prevention of persistently infected calves caused by Bovine Virus Diarrhea (BVD) virus types 1 and 2; as an aid in the prevention of abortion due to Infectious Bovine Rhinotracheitis (IBR) virus; for the prevention of urinary shedding of L. borgpetersenii serovar hardjo (type hardjo-bovis); as an aid in the prevention of respiratory disease caused by IBR virus, BVD virus types 1 and 2; and as an aid in reduction of infertility, delayed conception, or abortion caused by Campylobacter fetus var. venerealis, and leptospirosis caused by 5 serovars of Leptospira (L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae, and L. pomona).

A 12-month duration of immunity has been demonstrated against IBR-induced abortion and against disease, including persistently infected calves, caused by BVD types 1 and 2. In addition, vaccinated animals subsequently exposed to L. borgpetersenii serovar hardjo (type hardjo-bovis) have been shown to clear renal infections within 8 weeks of exposure.

This vaccine may be administered to pregnant cattle provided they were vaccinated, according to label directions, with any Express® FP vaccine within the past 12 months. May also be administered to calves nursing pregnant cows provided their dams were vaccinated within the past 12 months with Express FP products. See insert for details.

Composition: The product in the amber glass vial contains IBR and BVD Type 1 (Singer 1a cytopathic) and Type 2 (296 cytopathic) modified live viruses. The plastic vial contains C. fetus and the Leptospira organisms listed above, in an adjuvant system. Contains neomycin and thimerosal as preservatives.

Directions and Dosage: See insert.

This package contains one 10 dose vial of MLV vaccine and one 20 mL vial of bacterin diluent.