Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

EXPRESS® FP 5 Pr

BOEHRINGER

Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza 3-Respiratory Syncytial Virus Vaccine
Modified Live Virus
Veterinary Use Only

Indications: For vaccination of healthy cows and heifers prior to breeding for prevention of persistently infected calves caused by bovine viral diarrhea (BVD) virus types 1 and 2; as an aid in the prevention of abortion due to infectious bovine rhinotracheitis (IBR) virus; as an aid in the prevention of respiratory disease caused by IBR virus, BVD virus types 1 and 2, bovine respiratory syncytial virus (BRSV); as an aid in the reduction of respiratory disease caused by parainfluenza 3 (PI3) virus.

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.

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 any Express® FP vaccine. See below for details.

Composition: The product in the amber glass vial contains IBR, BVD type 1 (Singer 1a cytopathic) and type 2 (296 cytopathic), PI3, and BRSV modified live viruses. The plastic vial contains an adjuvanted diluent. Neomycin and thimerosal are used as preservatives.

Directions: Shake the accompanying bottle of adjuvanted diluent, then rehydrate the modified live virus vaccine by aseptically adding the adjuvanted diluent to the vaccine vial. Shake the rehydrated vaccine and use immediately.

Dosage: Using aseptic technique, inject 2 mL subcutaneously in front of the shoulder and midway of the neck, away from the suprascapular lymph node. If initial vaccination, repeat with any Express® vaccine containing BRSV modified live virus (MLV) in 14-28 days. Calves vaccinated before 6 months of age should be revaccinated at 6 months. A 2 mL booster dose is recommended annually. Cows and Heifers: Using aseptic technique, annually inject a single 2 mL dose subcutaneously at or about 4 weeks prior to breeding. Pregnant cows and nursing calves may be vaccinated following a pre-breeding vaccination. See Indications. If initial vaccination, see above.

Precautions: Store in dark at 2-7°C. Do not freeze. Use entire contents when first opened. Burn vaccine container and all unused contents. Do not vaccinate within 21 days before slaughter. Stressed cattle should not be vaccinated. Injection site swelling may occur. Anaphylactoid reactions may occur. Antidote: Epinephrine.

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 BJ 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 (0.81, 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 VIRUS	TREATMENT GROUP	PI POSITIVE	VIREMIA POSITIVE	LEUKOPENIA POSITIVE
BVDV type 1	Vaccinates	1/22 (4.5%)	0/22 (0%)	8/22 (36.4%)
	Controls	20/23 (87.0%)	19/23 (82.6%)	21/23 (91.3%)
BVDV type 2	Vaccinates	0/18 (0%)	1/18 (5.6%)	1/18 (5.6%)
	Controls	21/22 (95.5%)	20/22 (90.9%)	14/22 (63.6%)

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

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® VL5 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).

SUPPORTING DATA, FETAL PROTECTION STUDY (NONPREGNANT FEMALES)

Study design: A fetal protection study was performed using a serial of Express® FP 5 (IBR, BVD type 1, BVD type 2, PI3 and BRSV modified live virus rehydrated with water diluent) with the BVD 1 and 2 components at minimum immunizing antigen content.

Healthy Angus-cross heifers (N=55) were chosen for use in the trial based upon both negative antibody status and T cell mediated reactivity status to both BVD type 1 and BVD type 2. The heifers were randomly assigned to 4 treatment groups: Group 1A, 18 heifers, vaccinated/challenged BVD type 1; Group 1B, 10 heifers, placebo/challenged BVD type 1; Group 2A, 19 heifers, vaccinated/challenged BVD type 2; Group 2B, 8 heifers, placebo/challenged BVD type 2. Heifers were vaccinated with a single 2 mL subcutaneous dose of Express® FP 5 or placebo (sterile water) approximately 4 to 7 weeks prior to insemination. Pregnant heifers were challenged intranasally with heterologous strains of either type 1 or type 2 BVD on ~day 75 of gestation.

The heifers were followed for clinical signs and any signs of abortion. Viremia (measured by virus isolation) and leukopenia (defined as a 40% or greater drop in white blood cell counts compared to baseline level) were measured post-challenge in the heifers. Serum samples were obtained from the heifers for determination of antibody titres.

Results:

Viremia and Leukopenia results are shown in the following table:

TREATMENT GROUP	VIREMIA (# POSITIVE/TOTAL)	LEUKOPENIA (# POSITIVE/TOTAL)
1A/Vac/BVD1	1/18	1/18
1B/Plac/BVD1	9/10	4/10
2A/Vac/BVD2	0/19	0/19
2B/Plac/BVD2	8/8	7/8

Serum antibody titres are shown in the following table:

TREATMENT GROUP	DAY 0		DAY 49		DAY OF CHALLENGE	
	BVD1	BVD2	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	< 2	< 2	3444	147	1625	116
1B/Plac/BVD1	< 2	< 2	< 2	< 2	< 2	< 2
2A/Vac/BVD2	< 2	< 2	2572	150	1475	118
2B/Plac/BVD2	< 2	< 2	< 2	< 2	< 2	< 2

TREATMENT GROUP	DAY 14 POST-CHALLENGE		HARVEST DAY ~200 POST-VACCINATION	
	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	7019	745	2366	345
1B/Plac/BVD1	139	13	1644	265
2A/Vac/BVD2	37231	14289	7971	3202
2B/Plac/BVD2	30	193	347	6889

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

The heifers were sacrificed on ~day 150 of gestation (~200 days post-vaccination, ~75 days post-challenge) and the fetuses harvested. All heifers had a viable fetus at the time of sacrifice. Fetal tissues, including spleen, thymus, cerebellum, and heart blood, were tested by virus isolation for the presence of virus.

The results of virus isolations from the fetal tissues are shown in the table below:

TREATMENT GROUP	THYMUS	CEREBELLUM	SPLEEN	HEART BLOOD	FINAL OUTCOME (% PROTECTION)
1A/Vac/BVD1	0/18	0/18	0/18	0/18	100
1B/Plac/BVD1	10/10	10/10	10/10	10/10	n/a
2A/Vac/BVD2	1/19	1/19	1/19	1/19	95
2B/Plac/BVD2	8/8	8/8	8/8	8/8	n/a

Conclusion: Vaccination with Express® FP 5 gave excellent protection against development of persistently infected calves caused by Type 1 and Type 2 BVD.

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 IBR, BVD 1, BVD 2, PI3, and 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.

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 pre-colostral antibodies to bovine viral 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.

MANUFACTURED BY: Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Missouri 64506 U.S.A.
US Vet. Lic. No. 124

Manufactured for: Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario L7L 5H4
126710-05

PRESENTATION: 10 doses (20 mL) and 50 doses (100 mL)
CPN: 1230018.7

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

EXPRESS® FP 5/Somnugen® Pr

BOEHRINGER

Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza 3-Respiratory Syncytial Virus Vaccine
Modified Live Virus
Haemophilus Somnus Bacterin
Veterinary Use Only

Indications: For vaccination of healthy cows and replacement heifers prior to breeding for prevention of persistently infected calves caused by bovine viral diarrhea virus types 1 and 2. Four non-cytopathic BVD challenge viruses were used in five different challenge studies to determine the efficacy of this product in preventing persistently infected calves due to BVD types 1 and 2. The challenge viruses included two BVD type 1b and two BVD type 2 strains.

For vaccination of healthy, susceptible cattle as an aid in prevention of respiratory disease caused by infectious bovine rhinotracheitis (IBR) virus, bovine viral diarrhea virus (BVD) types 1 and 2, and bovine respiratory syncytial virus (BRSV), as an aid in reduction of respiratory disease caused by parainfluenza 3 (PI3) virus, and bovine respiratory syncytial virus (BRSV), and as an aid in the prevention of disease caused by *Haemophilus somnus*. This vaccine may be used in pregnant females or calves nursing pregnant females, provided the females were vaccinated pre-breeding according to label directions with any Express® FP vaccine with fetal protection indications.

Composition: The product in the amber glass vial contains IBR, BVD type 1 (Singer 1a cytopathic) and type 2 (296 cytopathic), PI3, and BRSV modified live viruses. The plastic vial contains H. somnus in an adjuvant system. Neomycin and thimerosal are used as preservatives.

Directions: Shake the accompanying bottle of bacterin diluent, then rehydrate the modified live virus vaccine by aseptically adding the diluent to the vaccine vial. Shake the rehydrated vaccine and use immediately.

Dosage: Using aseptic technique, inject 2 mL subcutaneously in front of the shoulder and midway of the neck, away from the suprascapular lymph node. If initial vaccination, repeat with any Express® vaccine containing *H. somnus* and BRSV modified live virus (MLV) in 14-28 days. Calves vaccinated before 6 months of age should be revaccinated at 6 months. A 2 mL booster dose is recommended annually. **Cows and Heifers:** Using aseptic technique, annually inject a single 2 mL dose subcutaneously at or about 4 weeks prior to breeding. Pregnant cows and nursing calves may be vaccinated following a pre-breeding vaccination. See Indications. If initial vaccination, see above.

Precautions: Store in dark at 2-7°C. Do not freeze. Use entire contents when first opened. Burn vaccine container and all unused contents. Do not vaccinate within 21 days before slaughter. Stressed cattle should not be vaccinated. Injection site swelling may occur. Anaphylactoid reactions may occur. Antidote: Epinephrine.

SUPPORTING DATA, FETAL PROTECTION STUDY (NONPREGNANT FEMALES)

Study Design: A fetal protection study was performed using a serial of Express® FP 5 (IBR, BVD type 1, BVD type 2, PI3 and BRSV modified live virus rehydrated with water diluent) with the BVD 1 and 2 components at minimum immunizing antigen content.

Healthy Angus-cross heifers (N=55) were chosen for use in the trial based upon both negative antibody status and T cell mediated reactivity status to both BVD type 1 and BVD type 2. The heifers were randomly assigned to 4 treatment groups: Group 1A, 18 heifers, vaccinated/challenged BVD type 1; Group 1B, 10 heifers, placebo/challenged BVD type 1; Group 2A, 19 heifers, vaccinated/challenged BVD type 2; Group 2B, 8 heifers, placebo/challenged BVD type 2. Heifers were vaccinated with a single 2 mL subcutaneous dose of Express® FP 5 or placebo (sterile water) approximately 4 to 7 weeks prior to insemination. Pregnant heifers were challenged intranasally with heterologous strains of either type 1 or type 2 BVD on ~day 75 of gestation.

The heifers were followed for clinical signs and any signs of abortion. Viremia (measured by virus isolation) and leukopenia (defined as a 40% or greater drop in white blood cell counts compared to baseline level) were measured post-challenge in the heifers. Serum samples were obtained from the heifers for determination of antibody titres.

Results:

Viremia and Leukopenia results are shown in the following table:

TREATMENT GROUP	VIREMIA (# POSITIVE/TOTAL)	LEUKOPENIA (# POSITIVE/TOTAL)
1A/Vac/BVD1	1/18	1/18
1B/Plac/BVD1	9/10	4/10
2A/Vac/BVD2	0/19	0/19
2B/Plac/BVD2	8/8	7/8

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

Serum antibody titres are shown in the following table:

TREATMENT GROUP	DAY 0		DAY 49		DAY OF CHALLENGE	
	BVD1	BVD2	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	< 2	< 2	3444	147	1625	116
1B/Plac/BVD1	< 2	< 2	< 2	< 2	< 2	< 2
2A/Vac/BVD2	< 2	< 2	2572	150	1475	118
2B/Plac/BVD2	< 2	< 2	< 2	< 2	< 2	< 2

TREATMENT GROUP	DAY 14 POST-CHALLENGE		HARVEST DAY ~200 POST-VACCINATION	
	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	7019	745	2366	345
1B/Plac/BVD1	139	13	1644	265
2A/Vac/BVD2	37231	14289	7971	3202
2B/Plac/BVD2	30	193	347	6889

The heifers were sacrificed on ~day 150 of gestation (~200 days post-vaccination, ~75 days post-challenge) and the fetuses harvested. All heifers had a viable fetus at the time of sacrifice. Fetal tissues, including spleen, thymus, cerebellum, and heart blood, were tested by virus isolation for the presence of virus.

The results of virus isolations from the fetal tissues are shown in the table below:

TREATMENT GROUP	THYMUS	CEREBELLUM	SPLEEN	HEART BLOOD	FINAL OUTCOME (% PROTECTION)
1A/Vac/BVD1	0/18	0/18	0/18	0/18	100
1B/Plac/BVD1	10/10	10/10	10/10	10/10	n/a
2A/Vac/BVD2	1/19	1/19	1/19	1/19	95
2B/Plac/BVD2	8/8	8/8	8/8	8/8	n/a

Conclusion: Vaccination with Express® FP 5 gave excellent protection against development of persistently infected calves caused by Type 1 and Type 2 BVD.

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 IBR, BVD 1, BVD 2, PI3, and 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.

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 pre-colostral antibodies to bovine viral diarrhea virus 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.

MANUFACTURED BY: Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Missouri 64506 U.S.A.
US Vet. Lic. No. 124

Manufactured for: Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario L7L 5H4
126805-04

PRESENTATION: 10 doses (20 mL) and 50 doses (100 mL)
CPN: 1230017.8

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

EXPRESS® FP 5-VL5 Pr

BOEHRINGER

Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza 3-Respiratory Syncytial Virus Vaccine
Modified Live Virus
Campylobacter Fetus-Leptospira Canicola-Grippotyphosa-Hardjo-Icterohaemorrhagiae-Pomona Bacterin
Veterinary Use Only

Indications: For vaccination of healthy cows and heifers prior to breeding for prevention of persistently infected calves caused by bovine viral 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, bovine respiratory syncytial virus (BRSV); as an aid in the reduction of respiratory disease caused by parainfluenza 3 (PI3) virus; 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 any Express® FP vaccine. See below for details.

Composition: The product in the amber glass vial contains IBR, BVD type 1 (Singer 1a cytopathic) and type 2 (296 cytopathic), PI3, and BRSV 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: 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 any Express® vaccine containing C. *fetus, Leptospira*, and BRSV modified live virus (MLV) 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 following the pre-breeding vaccination. See below for details. If initial vaccination, see above.

Precautions: Store in dark at 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. Injection site swelling or anaphylactoid reactions may occur. Antidote: Epinephrine.

Summary of BVD type 1 and 2 duration of immunity efficacy studies: Four non-cytopathic BVD challenge viruses were used in five different challenge studies to determine the efficacy of this product in preventing persistently infected calves due to BVD types 1 and 2. The challenge viruses included two BVD type 1b and two BVD 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

CHALLENGE VIRUS	TREATMENT GROUP	# POSITIVE/TOTAL	TOTAL PERCENT PROTECTED
BVDV type 1 (2 Studies)	Vaccinates	1 of 29	96%
	Controls	18 of 18	0%
BVDV type 2 (3 Studies)	Vaccinates	2 of 46	96%
	Controls	29 of 29	0%

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 BJ 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.

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

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 (0.81, 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 VIRUS	TREATMENT GROUP	PI POSITIVE	VIREMIA POSITIVE	LEUKOPENIA POSITIVE
BVDV type 1	Vaccinates	1/22 (4.5%)	0/22 (0%)	8/22 (36.4%)
	Controls	20/23 (87.0%)	19/23 (82.6%)	21/23 (91.3%)
BVDV type 2	Vaccinates	0/18 (0%)	1/18 (5.6%)	1/18 (5.6%)
	Controls	21/22 (95.5%)	20/22 (90.9%)	14/22 (63.6%)

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® VL5 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 intraocularly 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 vaccinates 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 vaccinates were negative, whereas the challenge organism was recovered from the kidneys of 10 of 11 (90.9%) placebo-control heifers.

Summary of Lepto hardjo-bovis studies

PARAMETER	TREATMENT GROUP	# POSITIVE/TOTAL	TOTAL PERCENT PROTECTED
Urine Shedding	Vaccinates	0 of 21	100%
	Controls	11 of 11	0%
Kidney Colonization	Vaccinates	0 of 21	100%
	Controls	10 of 11	9%

Culture results from weekly urine samples starting at 1 week post-challenge confirmed that vaccination prevented urinary shedding of the challenge organism. Kidney culture results confirmed that the vaccinated heifers were negative for kidney infection at 8 weeks post-challenge.

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 IBR, BVD 1, BVD 2, PI3, and 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

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

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.

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 pre-colostral antibodies to bovine viral 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 vaccination only. Accidental injection into humans can cause serious local reactions. Contact a physician immediately if accidental injection occurs.

MANUFACTURED BY: Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Missouri 64506 U.S.A.
US Vet. Lic. No. 124

Manufactured for: Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario L7L 5H4
128506-02

PRESENTATION: 10 doses (20 mL) and 50 doses (100 mL)
CPN: 1230127.2

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

EXPRESS® FP 10 Pr

BOEHRINGER

Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza 3-Respiratory Syncytial Virus Vaccine
Modified Live Virus
Leptospira Canicola-Grippotyphosa-Hardjo-Icterohaemorrhagiae-Pomona Bacterin
Veterinary Use Only

Indications: For vaccination of healthy cows and heifers prior to breeding for prevention of persistently infected calves caused by bovine viral 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, bovine respiratory syncytial virus (BRSV); as an aid in the reduction of respiratory disease caused by parainfluenza 3 (PI3) virus; and as an aid in reduction of 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 any Express® FP vaccine. See below for details.

Composition: The product in the amber glass vial contains IBR, BVD type 1 (Singer 1a cytopathic) and type 2 (296 cytopathic), PI3, and BRSV modified live viruses. The plastic vial contains *L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae*, and *L. pomona* in an adjuvant system. Neomycin and thimerosal are used as preservatives.

Directions: Shake the accompanying bottle of bacterin diluent, then rehydrate the modified live virus vaccine by aseptically adding the diluent to the vaccine vial. Shake the rehydrated vaccine and use immediately.

Dosage: Using aseptic technique, inject 2 mL subcutaneously in front of the shoulder and midway of the neck, away from the suprascapular lymph node. If initial vaccination, repeat with any Express® vaccine containing Leptospira and BRSV modified live virus (MLV) in 14-28 days. Calves vaccinated before 6 months of age should be revaccinated at 6 months. A 2 mL booster dose is recommended annually. **Cows and heifers:** Using aseptic technique, annually inject a single 2 mL dose subcutaneously at or about 4 weeks prior to breeding. Pregnant cows and nursing calves may be vaccinated following a pre-breeding vaccination. See Indications. If initial vaccination, see above.

Precautions: Store in dark at 2-7°C. Do not freeze. Use entire contents when first opened. Burn vaccine container and all unused contents. Do not vaccinate within 21 days before slaughter. Stressed cattle should not be vaccinated. Injection site swelling may occur. Anaphylactoid reactions may occur. Antidote: Epinephrine.

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 BJ 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 (0.81, 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 VIRUS	TREATMENT GROUP	PI POSITIVE	VIREMIA POSITIVE	LEUKOPENIA POSITIVE
BVDV type 1	Vaccinates	1/22 (4.5%)	0/22 (0%)	8/22 (36.4%)
	Controls	20/23 (87.0%)	19/23 (82.6%)	21/23 (91.3%)
BVDV type 2	Vaccinates	0/18 (0%)	1/18 (5.6%)	1/18 (5.6%)
	Controls	21/22 (95.5%)	20/22 (90.9%)	14/22 (63.6%)

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

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® VL5 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).

SUPPORTING DATA, FETAL PROTECTION STUDY (NONPREGNANT FEMALES)

Study Design: A fetal protection study was performed using a serial of Express® FP 5 (IBR, BVD type 1, BVD type 2, PI3 and BRSV modified live virus rehydrated with water diluent) with the BVD 1 and 2 components at minimum immunizing antigen content.

Healthy Angus-cross heifers (N=55) were chosen for use in the trial based upon both negative antibody status and T cell mediated reactivity status to both BVD type 1 and BVD type 2. The heifers were randomly assigned to 4 treatment groups: Group 1A, 18 heifers, vaccinated/challenged BVD type 1; Group 1B, 10 heifers, placebo/challenged BVD type 1; Group 2A, 19 heifers, vaccinated/challenged BVD type 2; Group 2B, 8 heifers, placebo/challenged BVD type 2. Heifers were vaccinated with a single 2 mL subcutaneous dose of Express® FP 5 or placebo (sterile water) approximately 4 to 7 weeks prior to insemination. Pregnant heifers were challenged intranasally with heterologous strains of either type 1 or type 2 BVD on ~day 75 of gestation.

The heifers were followed for clinical signs and any signs of abortion. Viremia (measured by virus isolation) and leukopenia (defined as a 40% or greater drop in white blood cell counts compared to baseline level) were measured post-challenge in the heifers. Serum samples were obtained from the heifers for determination of antibody titres.

Results:

Viremia and Leukopenia results are shown in the following table:

TREATMENT GROUP	VIREMIA (# POSITIVE/TOTAL)	LEUKOPENIA (# POSITIVE/TOTAL)
1A/Vac/BVD1	1/18	1/18
1B/Plac/BVD1	9/10	4/10
2A/Vac/BVD2	0/19	0/19
2B/Plac/BVD2	8/8	7/8

Serum antibody titres are shown in the following table:

TREATMENT GROUP	DAY 0		DAY 49		DAY OF CHALLENGE	
	BVD1	BVD2	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	< 2	< 2	3444	147	1625	116
1B/Plac/BVD1	< 2	< 2	< 2	< 2	< 2	< 2
2A/Vac/BVD2	< 2	< 2	2572	150	1475	118
2B/Plac/BVD2	< 2	< 2	< 2	< 2	< 2	< 2

TREATMENT GROUP	DAY 14 POST-CHALLENGE		HARVEST DAY ~200 POST-VACCINATION	
	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	7019	745	2366	345
1B/Plac/BVD1	139	13	1644	265
2A/Vac/BVD2	37231	14289	7971	3202
2B/Plac/BVD2	30	193	347	6889

The heifers were sacrificed on ~day 150 of gestation (~200 days post-vaccination, ~75 days post-challenge) and the fetuses harvested. All heifers had a viable fetus at the time of sacrifice. Fetal tissues, including spleen, thymus, cerebellum, and heart blood, were tested by virus isolation for the presence of virus.

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

The results of virus isolations from the fetal tissues are shown in the table below:

TREATMENT GROUP	THYMUS	CEREBELLUM	SPLEEN	HEART BLOOD	FINAL OUTCOME (% PROTECTION)
1A/Vac/BVD1	0/18	0/18	0/18	0/18	100
1B/Plac/BVD1	10/10	10/10	10/10	10/10	n/a
2A/Vac/BVD2	1/19	1/19	1/19	1/19	95
2B/Plac/BVD2	8/8	8/8	8/8	8/8	n/a

Conclusion: Vaccination with Express® FP 5 gave excellent protection against development of persistently infected calves caused by Type 1 and Type 2 BVD.

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 intraocularly 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 vaccinates 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 vaccinates were negative, whereas the challenge organism was recovered from the kidneys of 10 of 11 (90.9%) placebo-control heifers.

Summary of Lepto hardjo-bovis studies

PARAMETER	TREATMENT GROUP	# POSITIVE/TOTAL	TOTAL PERCENT PROTECTED
Urine Shedding	Vaccinates	0 of 21	100%
	Controls	11 of 11	0%
Kidney Colonization	Vaccinates	0 of 21	100%
	Controls	10 of 11	9%

Culture results from weekly urine samples starting at 1 week post-challenge confirmed that vaccination prevented urinary shedding of the challenge organism. Kidney culture results confirmed that the vaccinated heifers were negative for kidney infection at 8 weeks post-challenge.

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 intraocularly 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 vaccinates 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 vaccinates were negative, whereas the challenge organism was recovered from the kidneys of 10 of 11 (90.9%) placebo-control heifers.

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 IBR, BVD 1, BVD 2, PI3, and 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.

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

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 pre-colostral antibodies to bovine viral diarrhea virus 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.

MANUFACTURED BY: Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Missouri 64506 U.S.A.
US Vet. Lic. No. 124

Manufactured for: Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario L7L 5H4
127907-04

PRESENTATION: 5 doses (10 mL), 10 doses (20 mL), and 50 doses (100 mL).
CPN: 1230016.7

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

EXPRESS® FP 10/Somnugen® Pr

BOEHRINGER

Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza 3-Respiratory Syncytial Virus Vaccine,
Modified Live Virus
Haemophilus Somnus-Leptospira Canicola-Grippotyphosa-Hardjo-Icterohaemorrhagiae-Pomona Bacterin
Veterinary Use Only

Indications: For vaccination of healthy cows and replacement heifers prior to breeding for prevention of persistently infected calves caused by bovine viral diarrhea virus types 1 and 2.

For vaccination of healthy, susceptible cattle as an aid in prevention of respiratory disease caused by infectious bovine rhinotracheitis virus, bovine viral diarrhea virus types 1 and 2, and bovine respiratory syncytial virus; as an aid in reduction of respiratory disease caused by parainfluenza 3 virus and leptospirosis caused by *Leptospira canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae*, and *L. pomona*; as an aid in the prevention of disease caused by *Haemophilus somnus*. This vaccine may be used in pregnant females or calves nursing pregnant females, provided the females were vaccinated pre-breeding according to label directions with any Express® FP vaccine.

Composition: The product in the amber glass vial contains IBR, BVD type 1 (Singer 1a cytopathic) and type 2 (296 cytopathic), PI3, and BRSV modified live viruses. The plastic vial contains *H. somnus, L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae,* and *L. pomona* in an adjuvant system. Neomycin and thimerosal are used as preservatives.

Directions: Shake the accompanying bottle of bacterin diluent, then rehydrate the modified live virus vaccine by aseptically adding the diluent to the vaccine vial. Shake the rehydrated vaccine and use immediately.

Dosage: Using aseptic technique, inject 2 mL subcutaneously in front of the shoulder and midway of the neck, away from the suprascapular lymph node. If initial vaccination, repeat with any Express® vaccine containing *H. somnus, Leptospira*, and BRSV modified live virus (MLV) in 14-28 days. Calves vaccinated before 6 months of age should be revaccinated at 6 months. A 2 mL booster dose is recommended annually. **Cows and Heifers:** Using aseptic technique, annually inject a single 2 mL dose subcutaneously at or about 4 weeks prior to breeding. Pregnant cows and nursing calves may be vaccinated following a pre-breeding vaccination. See Indications. If initial vaccination, see above.

Precautions: Store in dark at 2-7°C. Do not freeze. Use entire contents when first opened. Burn vaccine container and all unused contents. Do not vaccinate within 21 days before slaughter. Stressed cattle should not be vaccinated. Injection site swelling may occur. Anaphylactoid reactions may occur. Antidote: Epinephrine.

SUPPORTING DATA, FETAL PROTECTION STUDY (NONPREGNANT FEMALES)

Study Design: A fetal protection study was performed using a serial of Express® FP 5 (IBR, BVD type 1, BVD type 2, PI3 and BRSV modified live virus rehydrated with water diluent) with the BVD 1 and 2 components at minimum immunizing antigen content.

Healthy Angus-cross heifers (N=55) were chosen for use in the trial based upon both negative antibody status and T cell mediated reactivity status to both BVD type 1 and BVD type 2. The heifers were randomly assigned to 4 treatment groups: Group 1A, 18 heifers, vaccinated/challenged BVD type 1; Group 1B, 10 heifers, placebo/challenged BVD type 1; Group 2A, 19 heifers, vaccinated/challenged BVD type 2; Group 2B, 8 heifers, placebo/challenged BVD type 2. Heifers were vaccinated with a single 2 mL subcutaneous dose of Express® FP 5 or placebo (sterile water) approximately 4 to 7 weeks prior to insemination. Pregnant heifers were challenged intranasally with heterologous strains of either type 1 or type 2 BVD on ~day 75 of gestation.

The heifers were followed for clinical signs and any signs of abortion. Viremia (measured by virus isolation) and leukopenia (defined as a 40% or greater drop in white blood cell counts compared to baseline level) were measured post-challenge in the heifers. Serum samples were obtained from the heifers for determination of antibody titres.

Results:

Viremia and Leukopenia results are shown in the following table:

TREATMENT GROUP	VIREMIA (# POSITIVE/TOTAL)	LEUKOPENIA (# POSITIVE/TOTAL)
1A/Vac/BVD1	1/18	1/18
1B/Plac/BVD1	9/10	4/10
2A/Vac/BVD2	0/19	0/19
2B/Plac/BVD2	8/8	7/8

Boehringer Ingelheim

BOEHRINGER INGELHEIM (CANADA) LTD.

5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4

CUSTOMER CARE NO. 1-800-567-1885
TECHNICAL SERVICES NO. 1-877-565-5501
WEBSITE: www.boehringer-ingelheim.ca

Serum antibody titres are shown in the following table:

TREATMENT GROUP	DAY 0		DAY 49		DAY OF CHALLENGE	
	BVD1	BVD2	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	< 2	< 2	3444	147	1625	116
1B/Plac/BVD1	< 2	< 2	< 2	< 2	< 2	< 2
2A/Vac/BVD2	< 2	< 2	2572	150	1475	118
2B/Plac/BVD2	< 2	< 2	< 2	< 2	< 2	< 2

TREATMENT GROUP	DAY 14 POST-CHALLENGE		HARVEST DAY ~200 POST-VACCINATION	
	BVD1	BVD2	BVD1	BVD2
1A/Vac/BVD1	7019	745	2366	345
1B/Plac/BVD1	139	13	1644	265
2A/Vac/BVD2	37231	14289	7971	3202
2B/Plac/BVD2	30	193	347	6889

The heifers were sacrificed on ~day 150 of gestation (~200 days post-vaccination, ~75 days post-challenge) and the fetuses harvested. All heifers had a viable fetus at the time of sacrifice. Fetal tissues, including spleen, thymus, cerebellum, and heart blood, were tested by virus isolation for the presence of virus.

The results of virus isolations from the fetal tissues are shown in the table below:

TREATMENT GROUP	THYMUS	CEREBELLUM	SPLEEN	HEART BLOOD	FINAL OUTCOME (% PROTECTION)
1A/Vac/BVD1	0/18	0/18	0/18	0/18	100
1B/Plac/BVD1	10/10	10/10	10/10	10/10	n/a
2A/Vac/BVD2	1/19	1/19	1/19	1/19	95
2B/Plac/BVD2	8/8	8/8	8/8	8/8	n/a

Conclusion: Vaccination with Express® FP 5 gave excellent protection against development of persistently infected calves caused by Type 1 and Type 2 BVD.

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 IBR, BVD 1, BVD 2, PI3, and 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.

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 pre-colostral antibodies to bovine viral diarrhea virus 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.

MANUFACTURED BY: Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Missouri 64506 U.S.A.
US Vet. Lic. No. 124

Manufactured for: Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario L7L 5H4
128007-04

PRESENTATION: 10 doses (20 mL) and 50 doses (100 mL)
CPN: 1230015.7