See productdata.aphis.usda.gov for a summary of the studies approved by the USDA for licensing this product. This package insert also contains additional information developed by the licensee.

Leptospira Hardjo Bacterin

Spirovac®

This product has been shown to be effective for the vaccination of healthy cattle, including pregnant cows and heifers, 4 weeks of age and older against disease caused by *Leptospira borgpetersenii* serovar Hardjo. A duration of immunity of at least 12 months has been demonstrated against renal infection and leptospiuria. For more information regarding efficacy and safety data, go to productdata.aphis.usda.gov.

This product has been shown to be effective against fetal, genital, and renal infections, and leptospiuria caused by *L. hardjo bovis*.

SAFETY AND EFFICACY: The safety of Spirovac was demonstrated in field studies representing different management practices in three different geographic locations in the United States. A total of 1431 beef and dairy cattle were evaluated where 615 calves (224 calves were below 4 1/2 weeks of age) and 816 cows (804 were pregnant) were vaccinated according to label recommendations. Safety in each trimester of pregnancy was established in dairy cows: 212 cows in the first trimester, 245 cows in the second trimester, and 144 cows in the third trimester. No systemic reactions or significant injection site reactions were observed in vaccinated animals.

The safety of an overdose of a Leptospira Hardjo-Pomona Bacterin (formulated as Spirovac but also containing *L. interrogans* serovar pomona) has been satisfactorily demonstrated in pregnant cattle. Seven pregnant cows in the first trimester of pregnancy and three in the second trimester of pregnancy were vaccinated with 6 times the recommended dose (twice the normal dose volume at three different injection sites). The cows were revaccinated in the same manner 28 days later. Despite the overdosing, only minor localized injection site reactions were observed, and no reaction exceeded 5.0 cm in diameter. No systemic reactions were observed and all ten cows were confirmed pregnant 30 days post second vaccination.

Researchers at the National Animal Disease Center (NADC) of the Agriculture Research Service (ARS), USDA, Ames, IA, conducted 2 separate studies evaluating the efficacy of Spirovac against the colonization of the urinary and reproductive tract of cattle when challenged with virulent strains of *L. borgpetersenii* serovar hardjo-bovis. The NADC challenge strains used in the studies are reliable in their ability to cause urinary shedding and represented the most common strains in the U.S. at the time. In the first study, heifers were vaccinated twice and challenged 16 weeks post second vaccination with serovar hardjo type hardjobovis 203 by intraperitoneal inoculation or conjunctival instillation for three consecutive days. Urine samples were collected weekly and heifers were euthanized 11–14 weeks postchallenge. Kidneys were examined for evidence of colonization. Leptospires were not detected in any of the urine or tissue samples from the Spirovac-vaccinated heifers, whereas 6/8 nonvaccinated heifers shed leptospires in their urine and all 8 had evidence of renal infection.

In the second study, 12 Spirovac-vaccinated and 12 nonvaccinated heifers were challenged 19 weeks postvaccination by instillation of either serovar hardjo type hardjobovis A (strain 203) or type hardjo-bovis B (strain 197) into the conjunctival sac and vagina. Cattle were monitored to detect urinary shedding of serovar hardjo for 8 weeks after challenge and the presence of leptospires in the uterus and oviducts was determined at necropsy. Urinary shedding of serovar hardjo was not detected in any (0/11) of the cattle vaccinated with Spirovac. In contrast, nonvaccinated cattle became infected and shed serovar hardjo in their urine (12/12).

Vaccinated cattle also were protected from colonization of the reproductive tract, whereas leptospires were detected in the uterus and/or oviducts of 10/12 control heifers.

The efficacy of Spirovac against placental and fetal infection was established in a study conducted by researchers at the NADC and Michigan State University which evaluated placental and fetal infection. Heifers were vaccinated two times prior to breeding and challenged at mid-gestation with virulent *L. borgpetersenii* serovar hardjo mixed strains 203 and 197 by conjunctival and vaginal instillation. Heifers were monitored for urinary shedding until calving. Heifers and calves and cows were euthanized as soon as possible after parturition and urine samples, maternal kidney, placenta and fetal tissues were examined to detect the presence of leptospires. Urinary shedding of serovar hardjo was detected in all (8/8) nonvaccinated control heifers and in none (0/16) of the vaccinated heifers after challenge. Leptospires were detected in the placenta or fetal tissues of 5/8 control cattle, whereas leptospires were not detected in any of the placenta or fetal tissues of the 16 Spirovac-vaccinated heifers.

A non-pivotal study was conducted to determine the effect of a Leptospira Hardjo-Pomona Bacterin (formulated as Spirovac but also containing *L. interrogans* serovar pomona) in young calves with maternally derived antibodies. A group of 12 calves from cows previously vaccinated were divided into 4 equal groups, with the first dose of Spirovac given at either 4, 6, 10, or 18 weeks of age and the second dose given 4 weeks after the first dose according to label recommendations for this supplemental study. Seven seronegative calves from unvaccinated cows were used as a control group. All calves were challenged at 30–32 weeks of age per intraperitoneal route. Microscopic agglutination titers (MAT) prevaccination ranged from 2 to 25, with maternal antibody titers observed for up to 13 weeks after birth. MAT titers were significantly higher in controls than vaccinates postchallenge. Serological titer rise in vaccinates were inversely proportional to prevaccination titers. Leptospiruria was not detected in any of the vaccinated calves but occurred in 71 percent of control calves within 21 days of challenge and in all controls by 35 days. This study showed that young calves vaccinated as early as 4 weeks of age were protected against a virulent challenge with *L. borgpetersenii* serovar hardjo-bovis strain 033.

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In a study conducted by researchers at the University of Massachusetts, NADC, and Michigan State University,[1] Spirovac was demonstrated to induce a strong, sustained cell-mediated immune response against *L. borgpetersenii* serovar hardjo. Spirovac induced production of gamma interferon and strong antigen-specific proliferative responses by peripheral blood mononuclear cells beginning 2 months after the first dose of vaccine and continuing for the 7-month study period. These responses were absent from nonvaccinated control cattle. A cell-mediated immune response is associated with protection against *L. borgpetersenii* serovar hardjo.

Duration-of-immunity study:
Twelve months duration-of-immunity was shown in a 54-week vaccination-challenge study. Eighteen 7- to 10-month-old calves were divided into 2 groups. Nine calves were vaccinated twice with Spirovac according to label recommendations at 4-week intervals and 9 calves were held as controls. The eighteen calves were housed together, held in isolation for 54 weeks, and subsequently challenged per intraperitoneal route with *L. borgpetersenii* serovar hardjo-bovis 033. Spirovac was shown to protect 100 percent of the vaccinated calves against urinary shedding (leptospiruria). It was concluded that Spirovac could provide protection for at least 12 months when administered according to label recommendations to healthy animals.

DIRECTIONS:
1. *General Directions*: Vaccination of healthy cattle is recommended. Shake well. Aseptically administer 2 mL subcutaneously. In accordance with Beef Quality Assurance guidelines, this product should be administered subcutaneously (under the skin) in the neck.

2. *Primary Vaccination*: Healthy cattle should receive 2 doses administered 4-6 weeks apart. When used to prevent genital or fetal infection, the second dose should be administered at least 2 weeks prior to breeding.

3. *Revaccination*: Historically, annual revaccination with this product has been recommended. The need for annual booster vaccinations has not been established for this product; consultation with a veterinarian or the manufacturer is recommended.

4. Good animal husbandry and herd health management practices should be employed.

PRECAUTIONS:
Store at 2°-8°C. Prolonged exposure to higher temperatures and/or direct sunlight may adversely affect potency. Do not freeze.

Use entire contents when first opened.

Sterilized syringes and needles should be used to administer this vaccine.

Do not vaccinate within 21 days before slaughter.

Contains thimerosal as a preservative.

As with many vaccines, anaphylaxis may occur after use. Initial antidote of epinephrine is recommended and should be followed with appropriate supportive therapy.

Do not mix with other products.

In case of human exposure, contact a physician.

REFERENCES:
1. Naiman BM, Alt DP, Bolin, CA, Zuerner R, Baldwin CL: Protective killed *Leptospira borgpetersenii* vaccine induces potent Th1 immunity comprising responses by CD4 and γδ T lymphocytes. *Infection Immun* 69:7550–7558, 2001.

Technical inquiries should be directed to Zoetis Inc. Veterinary Services, (888) 963-8471.

This product has been shown to be efficacious in healthy animals. A protective immune response may not be elicited if animals are incubating an infectious disease, are malnourished or parasitized, are stressed due to shipment or environmental conditions, are otherwise immunocompromised, or the vaccine is not administered in accordance with label directions.

For veterinary use only

VLN 190/PCN 26M7.01

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