

PFIZER INC.

PFIZER ANIMAL HEALTH

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VANGUARD® PLUS 5 L4

Pfizer Animal Health

Canine Distemper-Adenovirus Type 2-Parainfluenza-Parvovirus Vaccine

Modified Live Virus

Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterin

For use in dogs only

PRODUCT DESCRIPTION: Vanguard Plus 5 L4 is for vaccination of healthy dogs 6 weeks of age or older as an aid in preventing canine distemper caused by canine distemper (CD) virus, infectious canine hepatitis (ICH) caused by canine adenovirus type 1 (CAV-1), respiratory disease caused by canine adenovirus type 2 (CAV-2), canine parainfluenza caused by canine parainfluenza (CPI) virus, enteritis caused by canine parvovirus (CPV), and leptospirosis caused by *Leptospira canicola*, *L. grippotyphosa*, *L. icterohaemorrhagiae*, and *L. pomona*. Vanguard Plus 5 L4 is a freeze-dried preparation of attenuated strains of CD virus, CAV-2, CPI virus, CPV, and inactivated whole cultures of *L. canicola*, *L. grippotyphosa*, *L. icterohaemorrhagiae*, and *L. pomona*. These whole *Leptospira* cells have been extensively rinsed, resulting in reduced extraneous materials.

The CPV fraction is high titer ($>10^{7.0}$ TCID₅₀/dose) and was attenuated by low passage (35 passes from the canine isolate with a maximum of 2 additional passes allowed for production) on the canine cell line, which gives it the immunogenic properties capable of overriding maternal antibody interference at the levels indicated below. Some puppies in the field may have higher levels of maternal antibodies than those evaluated in our pivotal efficacy study. All viruses were propagated on established cell lines. An adjuvanted sterile gel is used to rehydrate the freeze-dried component, which is packaged with inert gas in place of vacuum.

SAFETY AND EFFICACY: Laboratory evaluation demonstrated that Vanguard Plus 5 L4 aided in preventing disease caused by CD, CAV-1, CAV-2, CPI, and CPV, and leptospirosis caused by *L. canicola*, *L. grippotyphosa*, *L. icterohaemorrhagiae*, and *L. pomona*, and that no significant immunologic interference existed among the vaccine fractions. Field safety trials conducted by Pfizer Animal Health showed it to be safe in dogs as young as 6 weeks of age under normal usage conditions.

It has been demonstrated that CAV-2 vaccine cross-protects against ICH caused by CAV-1. In addition, the CAV-2 strain used in Vanguard vaccines has been specially selected for freedom from oncogenic properties characteristic of adenoviruses.

Studies conducted at Pfizer demonstrated that the CAV-2 strain used in Vanguard vaccines not only protects against ICH, but against CAV-2 respiratory disease as well.¹ Although conventional CAV-1 (ICH) vaccines cross-protect against CAV-2, they may not prevent subclinical infection and spread of the CAV-2 agent. Canine adenovirus type 2 challenge virus was not recovered from CAV-2-vaccinated dogs in tests conducted at Pfizer.

The CPV fraction in Vanguard Plus 5 L4 was subjected to comprehensive safety and efficacy testing at Pfizer. It was shown safe and essentially reaction-free in laboratory tests and in clinical trials under field conditions. Product safety was further demonstrated by a backpassage study that included oral administration of multiple doses of the vaccine strain to susceptible dogs, all of which remained normal. The CPV virus in Vanguard Plus 5 L4 shares a characteristic with other live CPV vaccine strains in that the vaccine virus may be present in the feces following administration. Although this CPV vaccine virus was found occasionally and in low titers in the feces of vaccinated dogs, testing demonstrated that the vaccine master seed did not revert to virulence following 6 consecutive backpassages in susceptible dogs.

Research at Pfizer demonstrated that 3 doses of the vaccine with increased CPV virus titer can overcome serum neutralization (SN) titers associated with maternal antibody. Serum neutralization titers as low as 1:4 have been shown by others to interfere with active immunization using conventional modified live vaccines.^{2,3} A clinical trial was conducted

with fifty 6-week-old puppies [25 vaccinates (SN titer range <2-256) and 25 nonvaccinated controls (SN titer range 4-1024)]. The group of vaccinates received 3 doses, with vaccinations administered 3 weeks apart beginning at 6 weeks of age. After 1 vaccination, 13/25 puppies exhibited a 4-fold or greater increase in CPV SN titer (seroconversion). Twelve of these 13 puppies had maternal SN titers \leq 1:16 at the time of the first vaccination with the remaining puppy having an SN titer of 1:64. Another 9 puppies with initial SN titers between 1:16 and 1:256 seroconverted after the second vaccination. Their maternal antibody SN titers had declined to \leq 1:64 at the time of the second vaccination. Similarly, the last 3 vaccinates, with initial SN titers of 1:128, seroconverted after the third vaccination, after their maternal antibody CPV titer dropped \leq 1:64. Therefore, in this study, when 3 doses of vaccine were given beginning at 6 weeks of age, all 25 vaccinates, even those with the highest maternal antibody levels, became actively immunized (GM = 1:1176; range of SN titers 128-4096). All 50 dogs were challenged 3 weeks after the third vaccination with a heterologous CPV challenge virus. Fourteen of 25 nonvaccinated control dogs died or showed illness severe enough to warrant euthanasia, while all 25 vaccinates remained essentially healthy. The high-titer, low-passage vaccine virus in Vanguard Plus 5 L4 is therefore highly immunogenic and capable of stimulating active immunity in the presence of maternal antibodies.

DURATION OF SEROLOGIC RESPONSE: In dogs vaccinated and boosted as puppies, and then vaccinated again approximately 1 year later, revaccination with Vanguard Plus 5 L4 has been demonstrated (under field conditions) to result in serum antibody titers that persist for 12-48 months against CD virus (serum neutralization [SN] titer \geq 1:32), CAV-1 (SN \geq 1:16), CAV-2 (SN \geq 1:16), CPI virus (SN \geq 1:16), and CPV (hemagglutination inhibition [HAI] titer \geq 1:80).

Protection against infectious agents involves a complex interplay between humoral immunity, cellular immunity, or a combination of both. The purpose of vaccination is to induce effector cells in both these arms of the immune system. During the process, long-term immunity in the form of memory T and B lymphocytes is produced. Memory cells and antibodies interact to provide protection to an animal challenged with the same pathogen at a later date. Depending on the vaccine and the disease, antibodies may be produced that provide complete protection from disease and prevent or reduce shedding. In other cases, antibodies may play a minor or ineffective role and protection from disease relies on systemic, local cellular immunity and/or local antibody production. The role of sustained serological titers in the prevention of disease has not been confirmed.

In companion animals, immunological response to infection or vaccination has generally been evaluated by measuring the level of antibodies in serum and correlating these with protection or susceptibility. For the diseases caused by canine distemper virus, canine parvovirus, ^{4,5} canine adenovirus and leptospirosis, ⁴ evaluation of antibody titers may be a valuable diagnostic indicator to determine when revaccination may be needed. For other diseases, a serological response has not been identified that correlates with protection. Practical knowledge of the disease, the vaccine and the patient, along with serologic test results when appropriate, is paramount in making the best recommendation for a vaccination protocol for a specific animal.

The duration and character of the immune response to the viral antigens of Vanguard and/or Vanguard Plus were determined in a multi-center serology study involving 47 small animal veterinary clinics located in the United States (44) and Canada (3). Three hundred twenty-two male and female (intact and neutered) dogs of various ages, breeds, weights, lifestyles and time since last vaccination were enrolled in the study. Dogs were required to be healthy, greater than 2 years old with no history of disease due to CDV, CPV, CAV-1, CAV-2, or CPI and must not have been vaccinated for 12-48 months or longer. Additionally, dogs must have received at least a priming vaccination series approximately 2-7 weeks apart as a puppy and a booster vaccination approximately 8-16 months later. All previously administered vaccines were Vanguard products. A blood sample was collected from each dog and serum submitted to Cornell Veterinary Diagnostic Laboratory for determination of CDV (SN), CPV (HAI) titers, CAV-1 (SN), CAV-2 (SN), and CPI (SN). The samples were sent to a single diagnostic laboratory, thus ensuring a standardized test and methodology. As shown in the table below, elevated geometric mean titers were sustained for 12 to \geq 48 months after the last booster. Since the study was conducted under field conditions with client-owned animals, it is possible that natural exposure to infectious agents could have occurred without clinical signs of infection. In such cases, the titers measured in the study could be the result of exposure to the disease in addition to vaccinations during the course of the study.

Table 1. Geometric mean titer/number of dogs ⁶

Time Since Last Vaccination (Months)							
Antigen	12-18	19-24	25-30	31-36	37-42	43-48	>48
CDV	548/119	407/62	427/47	385/42	417/22	453/11	264/19
CPV	601/119	465/62	415/47	295/42	462/21	170/11	238/19
CAV-1	218/119	206/58	213/46	149/39	164/21	157/11	95/19
CAV-2	190/119	181/58	210/46	200/39	139/21	138/11	103/19
CPI	206/101	119/48	110/32	101/34	98/18	59/10	65/17

DIRECTIONS:

General Directions: Vaccination of healthy dogs 6 weeks of age or older is recommended. Aseptically rehydrate the

freeze-dried vaccine (Vanguard Plus 5 L4) with the sterile gel provided, shake well, and administer 1 mL subcutaneously or intramuscularly.

Primary Vaccination: Healthy dogs should receive 2 doses administered 3 weeks apart. To avoid the potential for maternal antibody interference, dogs vaccinated at less than 9 weeks of age should receive 3 doses, each administered 3 weeks apart.

Revaccination: Annual revaccination with a single dose is recommended, although, as recommended by the American Veterinary Medical Association and its Council on Biologic and Therapeutic Agents, the attending veterinarian should determine the frequency of revaccination based on the animal's lifestyle and risk of exposure.⁷

PRECAUTIONS:

Store at 2°-7°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 sterilize with chemicals because traces of disinfectant may inactivate the vaccine.

Burn containers and all unused contents.

Contains gentamicin as preservative.

Vaccination of pregnant bitches should be avoided.

In case of anaphylaxis, administer epinephrine or equivalent.

REFERENCES:

1. Bass EP, Gill MA, Beckenhauer WH: Evaluation of a canine adenovirus type 2 strain as a replacement for infectious canine hepatitis vaccine. *JAVMA* 177:234-242, 1980.
2. O'Brien SE, Roth JA, Hill BL: Response of pups to modified-live canine parvovirus component in a combination vaccine. *JAVMA* 188:699-701, 1986.
3. O'Brien SE: Serologic response of pups to the low-passage modified-live canine parvovirus-2 component in a combination vaccine. *JAVMA* 204:1207-1209, 1994.
4. Schultz RD: Current and future canine and feline vaccination programs. *Vet Med* 93(3):233-254, 1998.
5. Tizard I, Ni Y: Use of serologic testing to assess immune status of companion animals. *JAVMA* 213:54-60, 1998.
6. Study 2164H-60-01-004, Pfizer Animal Health
7. American Veterinary Medical Association, Position Statements on Biologics, June 2001.

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.

Technical inquiries should be directed to Pfizer Animal Health Veterinary Services, (800) 366-5288 (USA), (800) 461-0917 (Canada).

For veterinary use only

U.S. Veterinary License No. 189

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75-0671-02

Presentation: 50 x 1-dose trays.

NAC No.: 36902272