Your Dog's Arthritis Can Be Managed.

It All Starts With You.

Adequan® Canine
(POLYSULFATED GLYCOSAMINOGLYCAN)®

Managing Arthritis Is A
JOINT EFFORT

The Adequan® Canine (polysulfated glycosaminoglycan) JOINT EFFORT is grounded in the belief that canine arthritis can be managed. It is a partnership between you, your veterinarian and your dog—a partnership designed to promote proper joint health and a better quality of life for all dogs suffering from arthritis.

COULD YOUR DOG SUFFER FROM CANINE ARTHRITIS?

The answer is "yes." About 20 percent of all dogs in the U.S. suffer from canine arthritis. This disease develops gradually over time, causing your dog pain and often preventing him from performing even the simplest of movements, like climbing stairs or walking.

THE SIGNS OF CANINE ARTHRITIS

If your dog is suffering from arthritis, you will most likely see one or more of the following signs:

- Sluggishness
- Tiredness
- Low activity
- Reluctance to walking, running, climbing stairs, jumping or playing
- Lagging behind on walks
- Reluctance to extending rear legs
- Soreness
- Aggressive or withdrawn behavior
- Other personality or behavioral changes

THE RISK FACTORS OF CANINE ARTHRITIS

Canine arthritis can affect all breeds of dogs, but there are certain risk factors you should be aware of, including:

- Overweight dogs
- Large or giant breeds
- Over the age of 5
- Breed inherited traits, such as hip dysplasia
- Levels of high activity for long periods of time
- Joint trauma

UNDERSTANDING CANINE ARTHRITIS

Canine arthritis occurs in your dog's joints. A healthy joint consists of cartilage that covers and protects the ends of the bones in a joint. The cartilage has no nerves; when it touches the cartilage of another bone, the dog feels no pain.

However, arthritis causes the cartilage to wear away. This exposes the bone, which does have many nerves. So when two bones touch each other, your dog feels pain. This pain can greatly affect your dog's quality of life.

EARLY TREATMENT OF CANINE ARTHRITIS

When bones continually rub against each other, they will eventually change shape. The bone reshaping can make it difficult—or sometimes impossible—for your dog to walk or move naturally. Arthritis can be managed much more successfully when it is diagnosed and treated early in the process.

YOUR ROLE IN THE JOINT EFFORT

You know your dog better than anyone does. You see your dog everyday, and you are the best person to recognize the early signs and risk factors of canine arthritis. That's why you play such an important role in the Joint Effort.

The JOINT EFFORT Between You and Your Dog

Know how to spot the early signs of arthritis and the risk factors:

- Observe your dog for signs of arthritis
- Follow your veterinarian's treatment protocol
- Ask for Adequan® Canine to slow the disease of arthritis
- Take steps to maintain good joint health

The JOINT EFFORT Between You and Your Veterinarian

- Tell your veterinarian about signs you've observed and/or your dog's behavior changes
- Keep your veterinarian updated on your dog's progress
- Talk to your veterinarian about other ways to maintain good joint health

Managing joint health is a collaborative process resulting in a better quality of life for your dog.

Adequan® Canine (polysulfated glycosaminoglycan or PSGAG) should not be used in dogs who are hypersensitive to PSGAG or who have a known or suspected bleeding disorder. It should be used with caution in dogs with renal or hepatic impairment. Possible side effects (pain at injection site, diarrhea and abnormal bleeding) were mild, transient and self-limiting. Safety studies of PSGAG in breeding, pregnant or lactating dogs have not been conducted. See back cover for full product information.

ADEQUAN® CANINE Brand of Polysulfated Glycosaminoglycan Solution 100 mg/mL in a 5 mL preserved multiple dose vial for intramuscular use in dogs. **Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian. **Description:** The active ingredient in Adequan® Canine is polysulfated glycosaminoglycan (PSGAG). Polysulfated glycosaminoglycan is a semi-synthetic glycosaminoglycan prepared by extracting glycosaminoglycans (GAGs) from bovine tracheal cartilage. GAGs are polysaccharides composed of repeating disaccharide units. The GAG present in PSGAG is principally chondroitin sulfate containing 3 to 4 sulfate esters per disaccharide unit. The molecular weight for PSGAG used in the manufacture of Adequan® is 3,000 to 15,000 daltons. Each mL of Adequan® Canine contains 100 mg of PSGAG, 0.9% w/v benzyl alcohol as a preservative, and water for injection q.s. to 1 mL. Sodium hydroxide and/or hydrochloric acid added when necessary to adjust pH. **Pharmacology:** The specific mechanism of action of Adequan® in canine joints is not known. PSGAG is characterized as a "disease modifying osteoarthritis drug". Experiments conducted *in vitro* have shown PSGAG to inhibit certain catabolic enzymes which have increased activity in inflamed joints, and to enhance the activity of some anabolic enzymes. For example, PSGAG has been shown to significantly inhibit serine proteinases. Serine proteinases have been demonstrated to play a role in the Interleukin-I mediated degradation of cartilage proteoglycans and collagen. PSGAG is reported to be an inhibitor of Prostaglandin E2 (PGE2) synthesis. PGE2 has been shown to increase the loss of proteoglycan from cartilage. PSGAG has been reported to inhibit some catabolic enzymes such as elastase, stromelysin, metalloproteases, cathepsin B1, and hyaluronidases, which degrade collagen, proteoglycans, and hyaluronic acid in degenerative joint disease. Anabolic effects studied include ability to stimulate the synthesis of protein, collagen, proteoglycans, and hyaluronic acid in various cells and tissues *in vitro*. Cultured human and rabbit chondrocytes have shown increased synthesis of proteoglycan and hyaluronic acid in the presence of PSGAG. PSGAGs have shown a specific potentiating effect on hyaluronic acid synthesis by synovial membrane cells *in vitro*. Absorption,distribution, metabolism, and excretion of PSGAG following intramuscular injection have been studied in several species, including rats, rabbits, humans, horses and dogs. Studies in rabbits showed maximum blood concentrations of PSGAG following IM injection were reached between 20 to 40 minutes following injection, and that the drug was distributed to all tissues studied, including articular cartilage, synovial fluid, adrenals, thyroid, peritoneal fluid, lungs, eyes, spinal cord, kidneys, brain, liver, spleen, bone marrow, skin, and heart. Following intramuscular injection of PSGAG in humans, the drug was found to be bound to serum proteins. PSGAG binds to both albumin and chi- and beta-globulins and the extent of the binding is suggested to be 30 to 40%. Therefore, the drug may be present in both bound and free form in the bloodstream. Because of its relatively low molecular weight, the synovial membrane is not a significant barrier to distribution of PSGAG from the bloodstream to the synovial fluid. Distribution from the synovial fluid to the cartilage takes place by diffusion. In the articular cartilage the drug is deposited into the cartilage matrix. Serum and synovial fluid distribution curves of PSGAG have been studied in dogs and appear similar to those found in humans and rabbits. In rabbits, metabolism of PSGAG is reported to take place in the liver, spleen, and bone marrow. Metabolism may also occur in the kidneys. PSGAG administered intramuscularly and not protein bound or bound to other tissues is excreted primarily via the kidneys, with a small proportion excreted in the feces. **Toxicity:** In a subacute toxicity study, 32 adult beagle dogs (4 males and 4 females per treatment group) received either 0.9% saline solution or PSGAG at a dose of 5 mg, 15 mg, or 50 mg per kg of body weight (approximately 2.3, 6.8, or 22.7 mg/lb), via intramuscular injection twice weekly for 13 weeks. PSGAG doses represent approximately 1X, 3X, and 10X the recommended dosage of 2 mg/lb, and more than 3 times the recommended 4-week duration of treatment. Necropsies were performed 24 hours after the final treatment. During week 12, one dog in the 50 mg/kg dosage group developed a large hematoma at the injection site which necessitated euthanasia. No other mortalities occurred during the treatment period. Statistically significant changes in the 50 mg/kg group included increased prothrombin time, reduced platelet count, an increase in ALT and cholesterol, and increased liver and kidney weights. Increased cholesterol and kidney weights were also noted in the 15 mg/kg group. Microscopic lesions were noted in the liver (Kupffer cells containing eosinophilic foamy cytoplasm), kidneys (swollen, foamy cells in the proximal convoluted tubules), and lymph nodes (macrophages with eosinophilic foamy cytoplasm) in the 15 mg/kg and 50 mg/kg groups. Intramuscular inflammation, hemorrhage, and degeneration were seen in all 3 PSGAG treated groups; the incidence and severity appeareddose related. **Efficacy:** Efficacy of Adequan® Canine was demonstrated in two studies. A laboratory study using radiolabeled PSGAG established distribution of PSGAG into canine serum and synovial fluid following a single intramuscular injection of 2 mg/lb. A clinical field trial was conducted in dogs diagnosed with radiographically-confirmed traumatic and/or degenerative joint disease of 1 or 2 joints. Joints evaluated included hips, stifles, shoulders, hocks and elbows. Fifty-one dogs were randomly assigned to receive either Adequan® Canine at 2 mg/lb of body weight or 0.9% saline. Both treatments were administered by intramuscular injection twice weekly for 4 weeks (8 injections total). Investigators administering treatment and evaluating the dogs were unaware of the treatment assignment. A total of 71 limbs in 51 dogs were evaluated. Of these, 35 limbs in 24 dogs were in the Adequan® Canine treated group. Each lame limb was scored for lameness at a walk, lameness at a trot, pain, range of motion, and functional disability. The scores for the individual parameters were combined to determine a total orthopedic score. At the end of the treatment period, dogs treated with Adequan® Canine showed a statistically significant improvement in range of motion and total orthopedic score over placebo treated control dogs. **Indications and Usage:** Adequan® Canine is recommended for intramuscular injection for the control of signs associated with non-infectious degenerative and/or traumatic arthritis of canine synovial joints.**Contraindications:** Do not use in dogs showing hypersensitivity to PSGAG. PSGAG is a synthetic heparinoid; do not use in dogs with known or suspected bleeding disorders. **Reproductive Safety:** Studies to establish the safety of Adequan® Canine in breeding, pregnant, or lactating dogs have not been conducted. **Precaution:** Use with caution in dogs with renal or hepatic impairment. **Adverse Reactions:** In the clinical efficacy trial, 24 dogs were treated with Adequan® Canine twice weekly for 4 weeks. Possible adverse reactions were reported after 2.1% of the injections. These included transient pain at the injection site (1 incident), transient diarrhea (1 incident each in 2 dogs), and abnormal bleeding (1 incident). These effects were mild and self-limiting and did not require interruption of therapy. To report suspected adverse reactions or for a copy of the Material Safety Data Sheet for this product, contact Novartis Animal Health US, Inc. at 1-800-637-0281. **Human Warning:** Keep this and all medications out of reach of children. **Dosage and Administration:** The recommended dose of Adequan® Canine is 2 mg/lb body weight (.02 mL/lb, or 1 mL per 50 lb), by intramuscular injection only, twice weekly for up to 4 weeks (maximum of 8 injections). Do not exceed the recommended dose or therapeutic regimen. Do not mix Adequan® Canine with other drugs or solvents. **Storage Conditions:** Store at controlled room temperature up to 25°C (77°F) (See USP). **How Supplied:** Adequan® Canine Solution 100 mg/mL in a 5 mL preserved multiple dose vial.

Product ID # 97502 5mL Multiple Dose Vials Packaged 2 vials per box

Manufactured by:
LUITPOLD PHARMACEUTICALS, INC.
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Shirley, NY 11967
(631) 924-4000
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Marketed by:
NOVARTIS ANIMAL HEALTH US, INC.
Greensboro, NC 27408

NADA 141-038, Approved by FDA
Made in U.S.A.
Rev. 1/04 IN975
NAH/ADQ/VI/1 MG #12417

ADQ 050004B

[1] Source: Freedom of Information—NADA #141-038, Title: Controlled Field Trial

HOW YOUR VETERINARIAN CAN HELP

Your veterinarian will first examine your dog's medical history, followed by a thorough physical examination. Afterwards, your veterinarian may conduct one or more diagnostic tests.

Lameness Exam
An examination that helps identify joint lameness, pain, tenderness and swelling.

Radiographs (X-rays)
Your veterinarian can use X-rays to look for changes in the joint structure.

Magnetic Resonance Imaging (MRI)
An MRI produces a picture of the joint in order to determine how far arthritis has progressed.

Arthroscopy
Your veterinarian inserts a tube-like camera called an arthroscope into the joint. This surgical procedure is becoming increasingly available to diagnose arthritis.

DESTINATION: GOOD JOINT HEALTH

Now that you're part of the Joint Effort, it's time to start promoting good joint health in your dog. To ensure healthy joints for your dog:

- Reduce the overall amount of food at each meal
- Eliminate treats
- Participate in other low-impact exercises
- Take short leash walks or go swimming
- Minimize stair climbing
- Use portable ramps for getting in and out of cars
- Request a pain relieving medication
- Talk with your veterinarian about Adequan® Canine (polysulfated glycosaminoglycan), the only FDA-approved* disease modifying osteoarthritis drug that slows the progression of arthritis.

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*NADA #141-038, Approved by FDA

ADEQUAN® CANINE (polysulfated glycosaminoglycan) THE KEY TO JOINT HEALTH

Adequan® Canine (polysulfated glycosaminoglycan) is a prescription, water-based, intramuscular, polysulfated glycosaminoglycan (PSGAG) that helps prevent the cartilage in your dog's joint from wearing away. It helps keep the cartilage healthy and intact, so that the bone in the joint cannot touch other bones. No other drug for arthritis can do that.

HOW ADEQUAN® CANINE WORKS

Adequan® Canine is administered two times a week for four weeks. The drug is injected intramuscularly to ensure it reaches the critical parts of the joint. It goes to work in the joint in about two hours and stays in the joint for about three days.

With Adequan® Canine you should see signs of improvement within four weeks. Your dog may begin to act like the playful, active dog you remember.

A SAFE AND EFFECTIVE TREATMENT FOR ARTHRITIS

Numerous studies[1] show that Adequan® Canine stops the cartilage from breaking down and actually supports the repair process. And unlike nutritional supplements, Adequan® Canine is FDA-approved* and is the only drug of this type, so you can be assured of its safety and effectiveness.

JOIN TOGETHER FOR A JOINT EFFORT

Canine arthritis is a painful, debilitating disease, but it can be managed. Working with your veterinarian, you can help restore the healthy and enjoyable quality of life that your dog deserves.

For more information, please talk with your veterinarian.