Diagnosed with radiographically-confirmed traumatic and/or degenerative joint disease of 1 or more joints. Increased prothrombin time, reduced platelet count, and increased ALT were noted in the 50 mg/kg group. Mortalities occurred during the treatment period. Statistically significant changes in liver function tests and body weight were noted in the 50 mg/kg group. Increased cholesterol and kidney weights were noted in all groups, and the 50 mg/kg group developed a large hematoma at the injection site which necessitated euthanasia. No other significant changes were noted.

**Toxicity:**

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 more joints. Increased prothrombin time, reduced platelet count, and increased ALT were noted in the 50 mg/kg group. Mortalities occurred during the treatment period. Statistically significant changes in liver function tests and body weight were noted in the 50 mg/kg group. Increased cholesterol and kidney weights were noted in all groups, and the 50 mg/kg group developed a large hematoma at the injection site which necessitated euthanasia. No other significant changes were noted.

**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 of PSGAG 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% v/v benzyl alcohol as a preservative, and water for injection q.s. to 1 mL. Sodium hydroxide and/or hydrochloric acid was added when necessary to adjust pH.

**Pharmacology:**

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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 hirudinoid; do not use in dogs with known or suspected bleeding disorders.

Precautions: The safe use of Adequan® Canine used in breeding, pregnant, or lactating dogs has not been evaluated. 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.

Post Approval Experience (2014)
The following adverse events are based on voluntary, post-approval reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The signs reported are listed in decreasing order of reporting frequency.

Vomiting, anorexia, depression/lethargy, diarrhea.

In some cases, death has been reported.

To report suspected adverse drug events, contact Elanco US Inc. at 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

For technical assistance call Elanco US Inc. at 1-888-545-5973.

Warnings: Not for use in humans. 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 20° to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) (See USP Controlled Room Temperature).

How Supplied: Adequan® Canine Solution 100 mg/mL in a 5 mL preserved multiple dose vial.

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

Manufactured by: LUITPOLD PHARMACEUTICALS, INC. Animal Health Division Shirley, NY 11967 (631) 924-4000 1-800-458-0163

NADA 141-038, Approved by FDA

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