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. 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 to 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 body weight (approximately 2.3, 6.8, or 22.7 mg/lb). PSGAG doses were performed 24 hours after the final treatment. During week 12, one dog in the 50 mg/kg dosage group included increased prothrombin time, reduced platelet count, an increase in ALT and mortalities occurred during the treatment period. Statistically significant changes in the 50 mg/kg group developed a large hematoma at the injection site which necessitated euthanasia. No other toxicities were 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 appeared dose 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, 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.

**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 American Regent, Inc. at 1-800-458-0163. 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.

**Warnings:** Not for use in humans. Keep this and all medications out of reach of children.

**DOSAGE AND ADMINISTRATION:** Practice aseptic techniques in withdrawing each dose to decrease the possibility of post-injection bacterial infections. Adequately clean and disinfect the stopper prior to entry with a sterile needle and syringe. Use only sterile needles, and use each needle only once.

The vial stopper may be punctured a maximum of 10 times.

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). Avoid prolonged exposure to temperatures ≥40°C (104°F).

Use within 28 days of first puncture and puncture a maximum of 10 times. Dispose of spent needles in accordance with all federal, state and local environmental laws.

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

NDC 10797-975-02 5 mL Multiple Dose Vials Packaged 2 vials per box

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