Adequan® Canine
(polysulfated glycosaminoglycan)
A Disease-Modifying Osteoarthritis Drug

TECHNICAL BULLETIN

KEY POINTS

Introduction

For years, it's been commonly accepted that the prevalence of canine osteoarthritis (OA), also known as degenerative joint disease (DJD), is higher in aging dogs. However, OA can affect any breed of dog at any age. In fact, it's the most common cause of chronic pain in dogs,[1] and a recent study suggests that the prevalence of canine osteoarthritis is nearly 40 percent (n=188/500).[2] Canine osteoarthritis is genetic and can start early in a dog's life, often during the rapid growth stage that occurs in the first four to six months.

OA is a progressive disease with no known cure that can lead to chronic inflammation, irreversible joint damage, escalating pain and immobility. That's why there's a growing awareness of the need to rethink OA, look at a wider range of canine patients, and focus on early diagnosis and treatment.

Dog owner perception of changes in their dog's discomfort is a key component of early detection, but initial signs of OA can be subtle and are often overlooked. As one study notes:

> "Early intervention has the greatest potential for providing the most effective management of OA since it provides an opportunity to initiate an appropriate long-term care plan and disrupt the progressive, vicious cycle ..." [3]

The best way to manage OA is to diagnose it as early as possible to help slow down the disease. Once diagnosed, a proven treatment can alleviate some of the signs of OA and also help to slow or reduce the disease progression.

Polysulfated glycosaminoglycan (PSGAG) is characterized as a "disease-modifying osteoarthritis drug," which identifies Adequan® Canine. **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. **Select Important Safety Information:** Adequan Canine should not be used in dogs who are hypersensitive to PSGAG or have a known or suspected bleeding disorder.

The purpose of this technical bulletin is to explain the unique characteristics of Adequan Canine, the only FDA-approved disease-modifying osteoarthritis drug (DMOAD) clinically proven to treat the disease of OA.[4]

Adequan Canine®
polysulfated glycosaminoglycan

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The Impact of Adequan® Canine

(polysulfated glycosaminoglycan)

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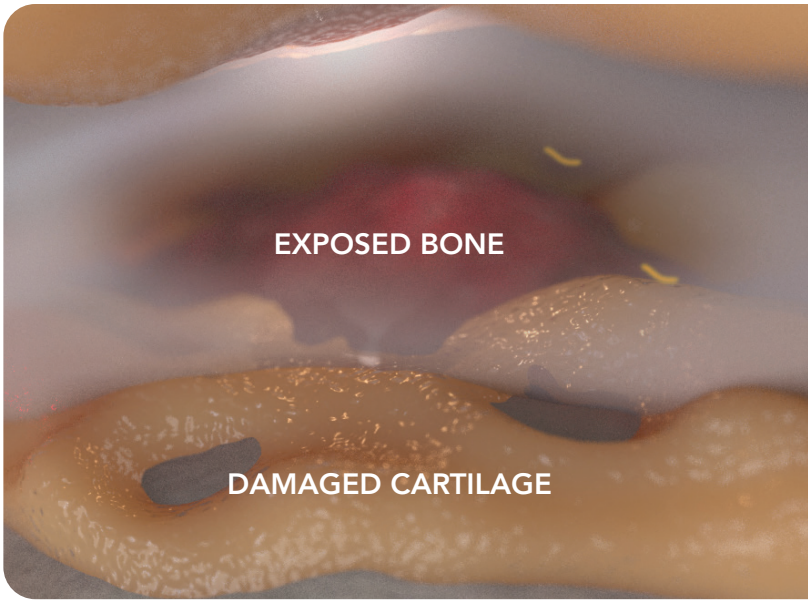
Slowing the progression of OA

Although OA is the most common cause of chronic pain in dogs,[1] it isn't just an "old dog" problem, as a myriad of studies have confirmed. OA clearly affects dogs of all ages. While any dog can develop the disease, some are at a higher risk than others. Breed, obesity, repetitive stress, injuries, infections, poor nutrition and genetics are known risk factors.

Active dogs need healthy cartilage to maintain effective joint function. In joints with osteoarthritis, the complex process of cartilage repair is unable to keep up with damage. Key components in the cartilage and synovial fluid are lost and not replaced. Over time, this can lead to bone-on-bone contact, chronic inflammation, swelling and escalating pain.

Unfortunately, owners may not notice changes in their dog's behavior or associate behavior changes with OA.[2] They may assume their dog is just tired after play or getting older. So they dismiss early signs and wait to seek help until their dog's symptoms are serious and debilitating. More education is needed to help dog owners learn how early treatment can slow down the clock, and what signs to look for and report to their veterinarian.

Currently, there is no known cure for canine OA, and its management has tended to focus on mitigating clinical signs (e.g., pain and inflammation) with symptom-modifying drugs or joint supplements. Although symptom-modifying treatments may alleviate signs of OA, they do not directly affect or help slow the progression of the disease. A disease-modifying osteoarthritis drug works differently. By definition, a DMOAD is capable of slowing and stabilizing the progression of osteoarthritis along with the damage it causes to joints.



As it progresses, OA can lead to exposed bone and cartilage damage. Over time, this leads to bone-on-bone contact, chronic inflammation, swelling, pain and loss of mobility.[1]

And there is one DMOAD approved for use by veterinarians for their canine patients: Adequan® Canine.

Select Important Safety Information: Adequan Canine should be used with caution in dogs with renal or hepatic impairment.

> Adequan® Canine (polysulfated glycosaminoglyan) is the only FDA-approved disease-modifying osteoarthritis drug (DMOAD) that inhibits cartilage loss in a dog's synovial joints. It's also the only pharmaceutical available that empowers veterinarians to proactively treat the disease and not just the signs of OA.[4]

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Mode of Action

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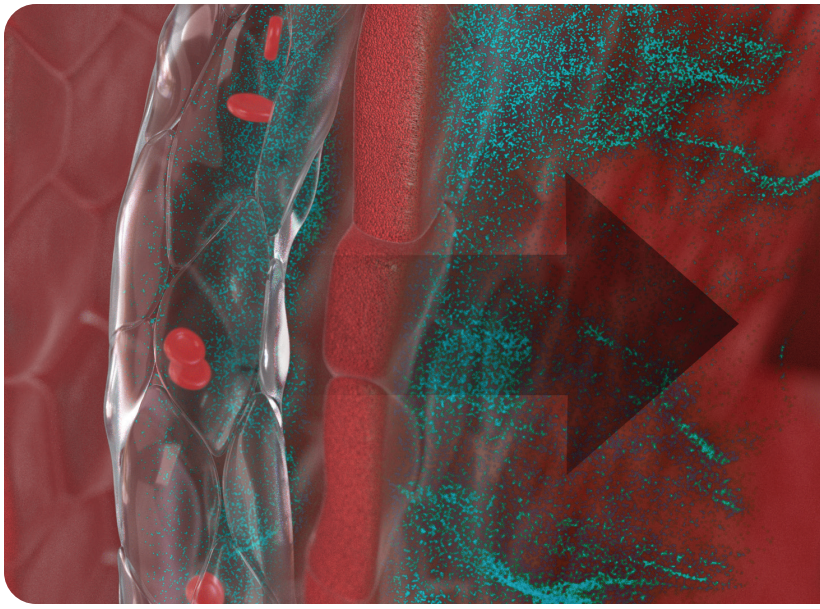
Mode of action

Adequan® Canine (polysulfated glycosaminoglycan) is an FDA-approved prescription drug to help reduce the loss of articular cartilage, slow the progression of joint structural damage, and promote healthy joint component maintenance. The specific mechanism of Adequan in canine joints is not known.[4] However, much is known from multiple published studies, which helps to explain its proven effects for dogs with OA.

Based on its approved indications for use, 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.[5]

Once Adequan Canine is injected, it enters the bloodstream, crosses the synovial membrane into the synovial fluid, and enters the articular cartilage by diffusion. It begins to reach joint synovial fluid within two hours and detectable levels are maintained in the synovial fluid and articular cartilage for up to three days (72 hours).[5]

Select Important Safety Information: Adverse reactions to Adequan Canine in clinical studies (transient pain at injection site, transient diarrhea, and abnormal bleeding) were mild and self-limiting.



Adequan® Canine enters the synovial membrane through the bloodstream.

Scan to view the Adequan® Canine mode of action video

Adequan Canine®
polysulfated glycosaminoglycan

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Proven Efficacy of Adequan® Canine

(polysulfated glycosaminoglycan)

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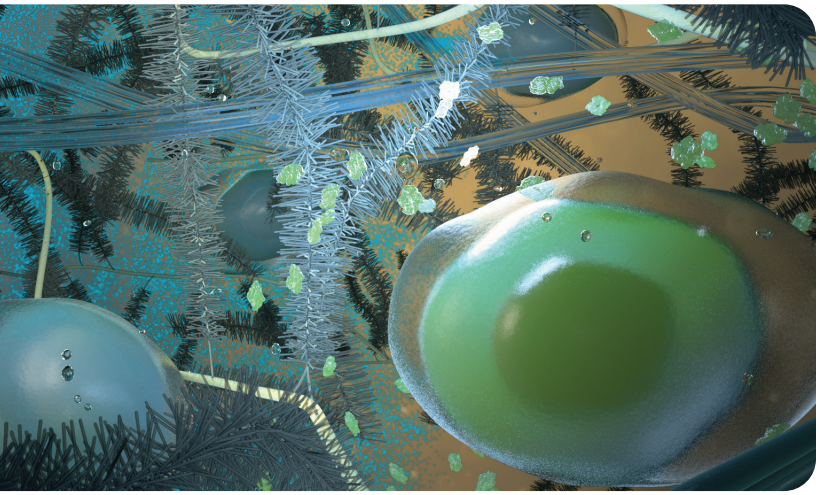
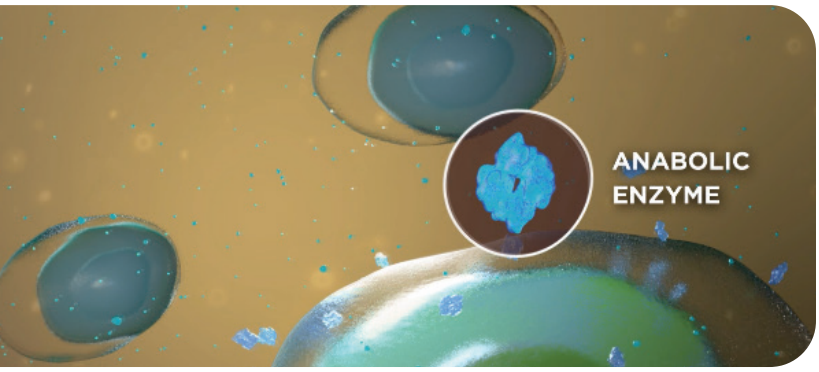


Adequan® Canine inhibits damaging enzymatic activity and loss of key joint components.



Adequan® Canine helps enhance enzymatic activity to promote a matrix rich in key components.

Select Important Safety Information: Adequan Canine in post approval experiences, death has been reported in some cases; vomiting, anorexia, depression/lethargy and diarrhea have also been reported.

Proven efficacy

Efficacy studies have shown Adequan® Canine (polysulfated glycosaminoglycan) inhibits the loss of key joint components, including:[4]

- Proteoglycan, a macromolecule that helps to form connective tissue.
- Collagen, a structural protein that's one of the major building blocks of bones, tendons and ligaments.
- Hyaluronic acid, an important lubricating molecule that helps to restore joint lubrication.

In vitro laboratory studies have confirmed that Adequan Canine inhibits catabolic enzymes that destroy these key molecules.

At the same time, Adequan Canine has been shown to enhance the activity of anabolic enzymes that help provide the valuable building blocks for cartilage repair in joints. This combination ultimately helps to renew damaged cartilage.

In a controlled field trial to determine efficacy and safety,[5] the Adequan Canine-treated group showed a trend toward greater improvement versus the placebo group for all seven key parameters:

- Lameness at a walk
- Gait analysis at a trot
- Pain on manipulation of limb
- Range of motion
- Functional disability
- Radiographic scoring
- Clinician's subjective response

Dogs (n=51) with radiographically detectable degenerative joint disease in one or two limbs were administered intramuscular injections twice weekly for 4 weeks (total of 8 injections). Dogs treated with Adequan Canine had statistically significant improvement in range of motion and orthopedic scores compared with placebo-treated control dogs.[5]

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Safety and Clinical Implications

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Safety/Toxicity

Dose selection for Adequan® Canine (polysulfated glycosaminoglycan) was based on published studies concerning the use of polysulfated glycosaminoglycan in osteoarthritis models in dogs. The selected dose of 2 mg/lb was shown to have an adequate margin of safety in dogs, and was confirmed in a clinical field trial. These results demonstrated that Adequan Canine, when used according to the conditions set forth in the labeling, is safe and effective.[5]

As noted on its label, studies to establish the safety of Adequan Canine in breeding, pregnant or lactating dogs have not been conducted.[5] Use with caution in dogs with renal or hepatic impairment.

Clinical implications for proactive management

As the most common chronic pain condition recognized in dogs,[1] osteoarthritis has garnered the attention of researchers, veterinary experts and orthopedic specialists for decades. More attention has brought an even greater understanding about the need to think earlier and younger and to be proactive in diagnosing and treating OA because, once cartilage wears away completely, it can't be restored. In order to help dogs stay as active as possible, for as long as possible, it's vital to focus on early diagnosis and treatment of OA to preserve articular cartilage.

> Early intervention has the greatest potential for providing the most effective management of OA since it provides an opportunity to initiate an appropriate long-term care plan and disrupt the progressive, vicious cycle of multidimensional deterioration.[3]

The day-to-day reality for dogs with OA is painful, and this has also led to a plethora of symptom-modifying options, such as NSAIDs, nutraceuticals and supplements predominantly focused on alleviating pain and observable clinical symptoms. While these products in a multimodal approach can provide temporary relief, they don't address the underlying cause or slow the progression of OA.

Adequan Canine is completely different, with its classification as a disease-modifying osteoarthritis drug (DMOAD) and the positive results it can deliver for dogs with OA.[4]

For more than 20 years, it has demonstrated the unique ability to help:[4]

- **restore joint lubrication**
- **relieve inflammation**
- **renew the building blocks of healthy cartilage**

In essence, as an integral part of the multimodal approach, Adequan Canine is proven to help slow the progression of the disease.

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At the Center of a Multimodal Approach

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The power of a multimodal plan

A treatment plan that combines a variety of therapies can be beneficial for your OA patients. While each patient is different, an effective multimodal treatment plan typically includes recommendations for weight control, exercise, adjunct therapies and pain management that all work together and help over time.

It's also vital to include the benefits of a DMOAD as early as possible. Adequan® Canine (polysulfated glycosaminoglycan) not only can alleviate the signs of OA but also reduces and helps to slow and stabilize the disease.

Physical therapy
Hydrotherapy
Laser therapy
Heat / Ice therapy

> There is tremendous benefit in diagnosing osteoarthritis earlier. Like most medical problems, we do a much better job treating them when we become aware of them before end-stage, before they become very severe. Diagnosing the problem early will let us implement a lot of different strategies that are going to modulate the problem over a long period of time. We'll be able to treat the problem in simpler ways, in less aggressive ways, in safer ways, in smarter ways. We'll have the opportunity to educate the owner over time.
>
> *Denis J. Marcellin-Little, DEDV, DACVS, DECVS, DACVSMR*

*Discover more about the benefits of early diagnosis and treatment of canine OA. Watch the **"Osteoarthritis (OA) Need For Early Diagnosis"** video.*

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Conclusion

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Conclusion

Many supplements and over-the-counter products may make similar claims to Adequan® Canine (polysulfated glycosaminoglycan). However, these products do not have the structured and qualified product testing and trials Adequan Canine completed to become the only FDA-approved DMOAD. Adequan Canine is clinically proven to help treat the disease, not just the symptoms. As an FDA-approved pharmaceutical, it is required to be prescribed by a licensed veterinarian, which offers the added assurance of the most accurate dosing, safe administration, and appropriate monitoring.

It's equally important to recognize that canine osteoarthritis is highly prevalent. Based on a recent clinical study,[2] the use of tools, such as an owner checklist, may help identify many previously undiagnosed dogs of all ages. In fact, developmental orthopedic conditions are the best predictor of OA and these begin to develop early in a dog's life.[6]

Early intervention of OA can be the most effective way to help manage the disease and mitigate its impact throughout a dog's life. A proactive approach is supported by FDA guidance, which emphasizes the need for diagnosis and treatments to inhibit the structural damage or target the underlying pathophysiology of OA to reduce pain and help slow the complications of joint damage, deterioration and failure.[7]

Adequan Canine can help meet that need because it's been proven to:

- Decrease inflammation of the synovial membrane, which is associated with the onset of osteoarthritis.
- Increase hyaluronic acid in the synovial fluid, which is needed to keep joints lubricated.

As the only FDA-approved DMOAD indicated to control clinical signs of OA, Adequan Canine offers unique advantages for veterinarians, their canine OA patients and clients. It is proven to help slow the progression of the disease, help reduce damage, and promote improved joint health and mobility.

Select Important Safety Information: The safe use of PSGAG in breeding, pregnant or lactating dogs has not been evaluated. **Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

References

1. M Epstein, K Kirkby Shaw. Osteoarthritis in Dogs and Cats: Novel Therapeutic Advances, *NAVC Proceedings*, 2016
2. A Wright, DM Amodie, N Cernicchiaro, BDX Lascelles, AM Pavlock, C Roberts & DJ Bartram. Identification of canine osteoarthritis using an owner-reported questionnaire and treatment monitoring using functional mobility tests. *Journal of Small Animal Practice* (2022) 63, 609-618. DOI: 10.1111/jsap.13500.
3. T Cachon, O Frykman, JF Innes, BDX Lascelles, M Okumura, P Sousa, F Staffieri, PV Steagall, B Van Ryssen. Face validity of a proposed tool for staging canine osteoarthritis: Canine OsteoArthritis Staging Tool (COAST), *The Veterinary Journal*, 235 (2018) 1-8.
4. Adequan® Canine (polysulfated glycosaminoglycan), Package Insert. American Regent, Inc.
5. Adequan® Canine (polysulfated glycosaminoglycan) NADA 141-038 FOI Summary, 1997.
6. Osteoarthritis in dogs. American College of Veterinary Surgeons. Accessed October 17, 2022. http://www.acvs.org/small-animal/osteoarthritis-in-dogs.
7. "Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry," U.S. Department of Health and Human Services, Food and Drug Administration. August 2018.

The difference between feeling better and getting better.®

Learn more about the FDA requirements for approval as a disease-modifying osteoarthritis drug (DMOAD). Download a copy of ***"Technical Bulletin: What is a DMOAD?"***

Please see safety information throughout this piece and the full prescribing Information on the back cover.

Adequan Canine®

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% v/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. The solution is clear, colorless to slightly yellow.

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 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, 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.

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 1-888-354-4857. 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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Rev. 9/2021

IN975
MG #44454

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