ABOUT ADEQUAN® CANINE

What is Adequan® Canine?
Adequan® Canine is the only FDA-approved disease-modifying osteoarthritis drug (DMOAD) for dogs. It is recommended for intramuscular injection for the control of signs associated with non-infectious degenerative and/or traumatic arthritis of canine synovial joints.

Adequan Canine Solution is a prescription formulation of polysulfated glycosaminoglycan (PSGAG). It is a DMOAD which inhibits cartilage loss in a dog’s joints.

Are there age or breed restrictions for Adequan Canine?
No age or breed restrictions; use in pregnant, breeding or lactating animals has not been evaluated.

How is Adequan Canine packaged?
Adequan Canine is a solution that is colorless to slightly yellow; 100 mg/mL in a 5 mL preserved multiple-dose vial, packaged 2 vials per box.

What is the dosage and administration?
2 mg/lb (.02 mL/lb or 1 mL/50 lb) by intramuscular injection only, twice weekly for up to 4 weeks (maximum of 8 injections).

How fast does Adequan Canine work?
It begins to work in the joint within 2 hours and stays in the joint for approximately 3 days.¹

What is the pharmacology of Adequan Canine?
- Low molecular weight allows the 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.
- PSGAG reaches synovial fluid within 2 hours of injection.¹
- Detectable levels are maintained in synovial fluid and articular cartilage for up to 72 hours.¹
- The specific mechanism of action of Adequan Canine in canine joints is not known.

MODE OF ACTION & EFFICACY

What is the Mechanism of Action for Adequan Canine?
The specific mechanism of action of Adequan Canine in joints is not known. In vitro research suggests PSGAG:
- Inhibits certain catabolic enzymes which have increased activity in inflamed joints.
- Enhances the activity of anabolic enzymes.
- Stimulates the synthesis of protein, collagen, proteoglycans and hyaluronic acid by chondrocytes and synoviocytes.
- Potentiates hyaluronic acid synthesis by synovial membrane cells.
- In the articular cartilage the drug is deposited into cartilage matrix and may help shield against further degradation.

What is the proof of efficacy for Adequan Canine?
Efficacy demonstrated in two studies, radiolabeled and clinical field trials.
- A study was conducted of the distribution of radiolabeled PSGAG into canine serum, synovial fluid and articular cartilage following a single IM injection of 2 mg/lb. Synovial fluid protein (an indicator of synovial inflammation) was significantly reduced in the shoulder joint.¹
- Field trial: Dogs with radiographically detectable degenerative joint disease in one or two limbs were administered IM 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.¹

For additional Pharmacology and Efficacy information, see the Full Prescribing Label on page 4.
HOW TO USE: PROTOCOL

Can I give Adequan Canine to a dog already taking an NSAID?
Luitpold Animal Health (LAH) has not completed any trials or studies identifying the combination use of NSAIDs and Adequan Canine.

What is the treatment protocol for a new patient starting with Adequan® Canine?
The approved label dose of Adequan Canine is 2 mg/lb body weight (.02 mL/lb or 1 mL/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. Be sure to 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.

What is the treatment protocol after the first 8 injections?
The approved label 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). We have no further studies or technical data supporting a use protocol beyond the approved label dosing.

Do I have to keep Adequan Canine refrigerated?
No, Adequan Canine needs to be stored at 68° to 77° F (20° to 25° C) with excursions permitted to 59° to 86° F (15° to 30° C). You need to avoid prolonged exposure to temperatures greater or equal to 104° F (40° C).

Can I give Adequan Canine subcutaneously instead of by intramuscular injection?
Adequan Canine is approved only for intramuscular injection.

Is Adequan Canine in a multiple-use vial?
Yes, Adequan Canine contains a preservative, which allows for multiple punctures of an individual vial. A product vial must be used within 28 days of first puncture and is limited to a maximum puncture of 10 times. Please properly dispose of spent needles in accordance with all federal, state and local environmental laws.

HOW DOES ADEQUAN CANINE COMPARE?

What is the difference between FDA-approved prescription Adequan Canine and other over-the-counter products?
There are many supplements and over-the-counter products making similar claims to Adequan Canine. However, these products are only supported by statements and do not have the structured and qualified product testing and trials Adequan Canine completed to obtain FDA-approval.

Adequan Canine is the only FDA-approved disease-modifying osteoarthritis drug for use in dogs and is recommended for the control of signs associated with non-infectious degenerative and/or traumatic arthritis of canine synovial joints.

SAFETY INFORMATION

Are there any Contraindications?
Do not use in dogs showing a hypersensitivity to PSGAG. PSGAG is a synthetic heparinoid; do not use in dogs with known or suspected bleeding disorders.

Any 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.

What is the current ISI (Important Safety Information) statement?
Adequan Canine 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. Adverse reactions in clinical studies (transient pain at injection site, transient diarrhea, and abnormal bleeding) were mild and self-limiting. In post approval experience, death has been reported in some cases; vomiting, anorexia, depression/lethargy and diarrhea have also been reported. The safe use of PSGAG in breeding, pregnant or lactating dogs has not been evaluated. For additional safety information, please Click Here for Full Prescribing Information.
ABOUT LUITPOLD ANIMAL HEALTH
The manufacturer of Adequan® Canine

Why is this change with Adequan® Canine occurring?
Adequan® Canine, a product you’ve trusted for more
than 20 years is now being distributed by its manufacturer,
Working with distribution partners, we’re now able to
distribute the product and provide technical and customer
support as well, to help advance joint health in dogs.

When does this change take place?
April 1, 2018

Will there be any delay in obtaining product in transition?
We do not anticipate any supply issues during the transition.

HOW TO PURCHASE
How can I order Adequan Canine?
Your Adequan Canine needs will still be serviced through
a wide network of authorized veterinary distributors.
Please go to the LAH website or call LAH at 800-458-0163.

Will the veterinary pricing change?
While we do not anticipate any pricing changes, please check
with your distributor. LAH does not set the pricing structure
to veterinarians from our distribution partners.

Can veterinarians or pet owners purchase Adequan Canine
directly from Luitpold Animal Health?
We have established a wide network of distributors that
make purchase easy. If you want to buy directly from LAH,
we can have our National Key Accounts Manager reach out
to you to discuss options. And since this is a prescription-
only product, pet owners must purchase through a licensed,
practicing veterinarian, not directly through LAH.

When is Adequan Canine available for sale from
Luitpold Animal Health’s distribution partners?
The transition of LAH becoming the official marketing
distributor of Adequan Canine will be April 1, 2018,
however the product availability through your distributor
should be a seamless transition and uninterrupted.

What happens to my pending orders for Adequan Canine
prior to the April 1 transition?
Please contact the local distributor where you placed
your order. They will be the best source of information
on your current and pending orders.

How do I return expired product after March 31?
Short-dated or expired Adequan Canine product should
be returned to the distributor that originally supplied the
product, per the established return policies. Contact your
distributor or Luitpold Animal Health at 800-458-0163.

ABOUT REBATES
Will client rebates offered before the April 1, 2018
transition still be redeemable?
Yes, the rebates provided prior to the April 1, 2018 transition
will be honored for purchases completed on or before
3/31/2018 and requests must be received on or before
6/1/2018. LAH is evaluating the program, look for more
details later.

FOR MORE INFORMATION
Where can I get a pet owner brochure?
We are working through the transition of all support materials
needed to assist your continued use of Adequan Canine,
including pet owner brochures. To learn more, please visit
adequancanine.com or contact LAH at 800-458-0163.

Where can I get a scientific paper, more information,
a publication or a monograph?
Visit adequancanine.com to learn more on the latest
available technical information or call Medical Affairs
at 888-354-4855.

Will this transition affect my clients or their dogs that
are already on Adequan Canine?
The availability of Adequan Canine should experience no
delays or interruptions with this transition.

Who can I call with questions about Adequan Canine?
To speak to a customer service representative, please call
800-458-0163 Monday-Friday, 8 a.m. to 6 p.m. ET or email
cs@luitpold.com. For Technical questions, call Medical Affairs
at 888-354-4855 Monday-Friday, 9 a.m. to 5 p.m. ET. To report
an adverse event, call 800-734-9236 or email pv@luitpold.com.

Is there a website?
Yes, you can learn more at adequancanine.com.

1. Adequan® Canine (polysulfated glycosaminoglycan) NADA 141-038
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 osteoarthritic 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-1 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, metalloproteinases, 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. Based on its relatively low molecular weight, the synovial membrane is 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 promptly washed away was bound or bound to other tissues is excrated 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/kg), via intramuscular injection twice weekly for 13 weeks. PSGAG doses represent approximately 1X, 3X, and 10X the recommended dosage of 2 mg/kg, 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 3 all PSGAG treated groups; the incidence and severity appeared dose related.

Efficacy: Efficacy of Adequan® Canine was demonstrated in two studies. A laboratory study using radiosabeled PSGAG established the distribution of PSGAG in canine serum and synovial fluid following a single intramuscular injection of 2 mg/kg. 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/kg 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 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 Luitpold Pharmaceuticals, 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 (0.02 mL/lb, or 1 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.