

ADEQUAN CANINE- polysulfated glycosaminoglycan injection, solution
Elanco US Inc.

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% 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.

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-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. 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 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

Marketed by:
ELANCO US INC.
2500 Innovation Way
Greenfield, IN 46140



NADA 141-038, Approved by FDA

Made in U.S.A.

Rev. 2/16

IN975
MG #12417

PA100090AMX

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Package Label.Principal Display Panel - Container

Product ID # 97502

Adequan[®] Canine
(Polysulfated Glycosaminoglycan)

100 mg/mL 5 mL Preserved Multiple Dose Vial
FOR INTRAMUSCULAR USE IN DOGS

Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).
See package insert for full directions.

Rev. 2/16

Manufactured by: Luitpold Pharmaceuticals, Inc.
Animal Health Division, Shirley, NY 11967

Marketed by: Elanco US Inc.

Greenfield, IN 46140

NADA 141-038
Approved by FDA

YL100090AMX

Adequan[®] Canine
Polysulfated Glycosaminoglycan[®]
100 mg/mL 5 mL Preserved Multiple Dose Vial
FOR INTRAMUSCULAR USE IN DOGS
Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).
See package insert for full directions. Rev. 2/16

Product ID # 97502

Manufactured by: Luitpold Pharmaceuticals, Inc.
Animal Health Division, Shirley, NY 11967

Marketed by: Elanco US Inc.
Greenfield, IN 46140

NADA 141-038,
Approved by FDA

YL100090AMX

Lot / Exp.

Package Label.Principal Display Panel - Carton

Product ID # 97502

Adequan[®] Canine
(POLYSULFATED GLYCOSAMINOGLYCAN)

PSGAG
Sterile Injection
100 mg/mL (500 mg/5 mL)

FOR VETERINARY USE ONLY

Box Containers Two 5 mL Preserved Multiple Dose Vials

ELANCO
NADA 141-038, Approved by FDA

Marketed by: Elanco US Inc., 2500 Innovation Way, Greenfield, IN 46140 1-888-545-5973



ADEQUAN CANINE

polysulfated glycosaminoglycan injection, solution

Product Information

Product Type	PRESCRIPTION ANIMAL DRUG	Item Code (Source)	NDC:58 198-0975
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
POLYSULFATED GLYCOSAMINOGLYCAN (UNII: 268AW7000T) (POLYSULFATED GLYCOSAMINOGLYCAN - UNII:268AW7000T)	POLYSULFATED GLYCOSAMINOGLYCAN	100 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZYL ALCOHOL (UNII: LKG8494WBH)	
WATER (UNII: 059QF0K00R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:58 198-0975-1	2 in 1 CARTON		
1		5 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA141038	07/01/1997	

Labeler - Elanco US Inc. (966985624)

Registrant - Luitpold Pharmaceuticals, Inc. (002033710)

Establishment

Name	Address	ID/FEI	Business Operations
Daiichi Sankyo Altrich Sari		262417595	API MANUFACTURE

Revised: 8/2016

Elanco US Inc.