

CARTROPHEN VET



A Disease Modifying Osteoarthritis Drug

CARTROPHEN VET (pentosan polysulfate) is a treatment for osteoarthritis that provides pain relief by acting on the pathology within the joint that causes the pain. It also protects and supports the recovery of joint cartilage that is damaged by the arthritic process. CARTROPHEN VET has therefore been classified as a disease modifying osteoarthritis drug (DMOAD) and represents the rational approach to the medical treatment of osteoarthritis in dogs.

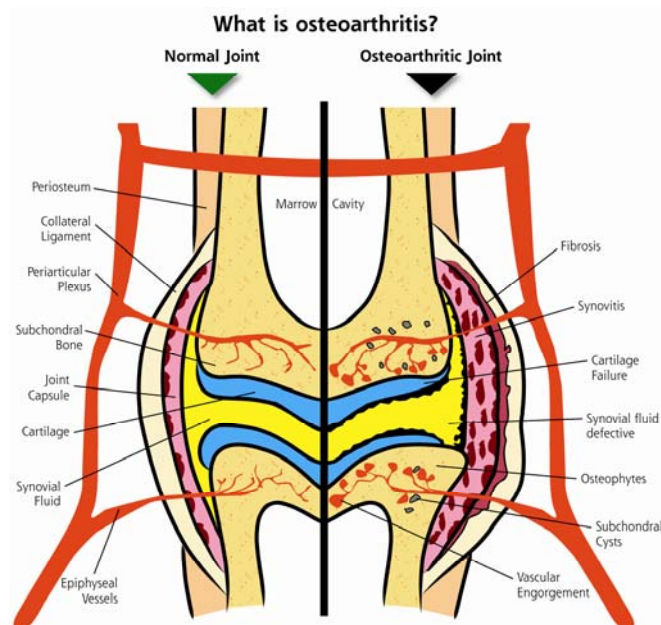
Cartrophen
VET

www.arthritis.au.com

The degenerative effects of osteoarthritis on the joint.

Articular cartilage and synovial fluid are essential components for the optimum mechanical performance of synovial joints, and the failure of these tissues in the various arthritides is contributory to the perpetuation of this group of diseases.

In normal "healthy" joints, the articular cartilage which covers the ends of the long bones, in conjunction with synovial fluid, provides an almost frictionless, wear resistant, weight-bearing surface. The articular cartilage also dissipates most of the contact stresses acting across diarthrodial joints during loading, thereby more evenly distributing the forces which are transmitted through subchondral bone. Synovial fluid is often decreased in quality (viscosity) in osteoarthritis (OA) due to defective hyaluronic acid synthesis and increased catabolism. This leads to a decrease in lubrication and stabilisation of the joint resulting in additional cartilage trauma and wear. There is hypoxia, decreased pH, and accumulation of lactate in synovial fluid of arthritic joints.



An early event in the pathogenesis of OA is softening and fibrillation of articular cartilage. This results in a decline in its functional capacity and, under normal weight-bearing conditions, abnormally high contact stresses are transmitted to focal areas of the articular cartilage and subchondral bone, exacerbating the damage to these tissues. The cartilage fragments and matrix degradation products (e.g. from proteoglycans and Type II collagen) released from the damaged articular cartilage are antigenic and when they localise in the synovial membrane, they can provoke an inflammatory response (synovitis). Once the synovitis becomes established in the joint, the synovial lining cells together with leucocytes recruited from the blood, release a host of noxious substances which can perpetuate the OA processes. These include proteinases, prostaglandins, cytokines (IL-1, TNF- α) and free radicals, all of which can directly and indirectly degrade cartilage, bone and the hyaluronic acid of synovial fluid.

Cartilage derived antigens released into synovial fluid can also activate blood leucocytes to express pro-coagulant and cytokine activities. This may result in deposition of lipid and fibrin clots in synovial tissues and in the small blood vessels supplying the subchondral bone. When blood flow and nutrition to bone and synovial cells is compromised by these occlusions the result is ischaemia, cell necrosis and joint pain. Furthermore, in response to the cellular necrosis and trauma, there is remodelling and thickening of subchondral bone altering its mechanical compliance. This increases the load-bearing stresses carried by the overlying articular cartilage, thereby subjecting it to excessive mechanical stresses. These mechanical factors all contribute to cartilage failure in OA.

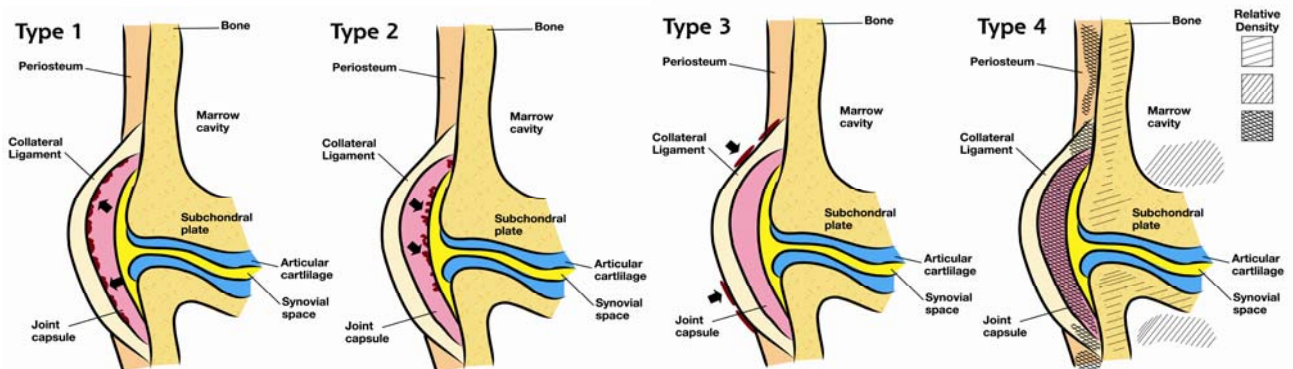
A variety of therapeutic agents are available for the treatment of OA but steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) are the most extensively used today. While the potent anti-inflammatory and analgesic activities of these agents may reduce the symptoms arising in OA joints, chronic use of some NSAIDs and corticosteroids have been reported to accelerate joint destruction largely due to the inhibition of cellular anabolic processes. The adverse effects of NSAIDs on the gastrointestinal tract, liver and kidney are well documented.

Osteoarthritis and pain.

Pain in OA is the most important clinical sign in humans and domestic animals. Pain is the principle cause of reduced performance and its pathogenesis is usually multifactorial. Control of pain is a key objective in the management of OA, however, this must be balanced with the important role the peripheral neuroanatomy of joints and pain plays in preventing further damage. In addition, the other objectives of OA treatment must also be addressed, including (1) regain normal joint function, (2) prevent cartilage destruction, (3) prevent fibrosis to preserve joint range of motion, (4) control inflammation, (5) prevent subchondral bone changes and osteophyte formation, (6) maintain a normal biochemical environment within the joint and (7) preserve synovial fluid viscosity and chemical makeup. McLaughlin R (2000). *Vet. Clin. North Am: Sm. Anim. Pract.* 30: 933-949.

Schematic representation of the location and distribution of articular nerve endings

[from Caron JP (1996). In "Joint Disease of the Horse", editors CW. McIlwraith and GW. Trotter, WB. WB Saunders Company, Philadelphia, p71]



The peripheral neuroanatomy of joints is reported to be similar in many species and the popular classification of articular nerve endings in mammalian appendicular joints is four receptor types - types 1, 2, 3 and 4. Note the absence of nerve tissue in articular cartilage.

- (A) Type 1 - mechanoreceptors located in the superficial areas of the joint capsule; low-threshold and stimulated by relatively mild mechanical stimuli; remain active while a mechanical stimuli persists;
- (B) Type 2 - mechanoreceptors located more deeply in the joint capsule; low-threshold and rapidly adapting; inactive when joints are immobile and activated when joints undergo movement or experience tension;
- (C) Type 3 - mechanoreceptors are large and are restricted to intra-articular and periarticular ligaments near their insertions; high-threshold and slowly adapting; inactive in stationary joints and with active and passive movement over a limited range; activated only when joint excursions occur near physiological limits or when ligaments containing them undergo powerful traction forces; capable of nociception and modifying type 1 and 2 receptor-mediated reflexes; and
- (D) Type 4 - 'receptors' are free nerve endings rather than specific end organs like receptors 1 to 3 of which there are two types - type 4a and 4b; high threshold and slowly adapting nociceptors; activation signals impending or actual tissue damage; are polymodal and respond to mechanical, heat and chemical stimuli such as lactic acid, kinins, serotonin, histamine and prostaglandin E₂.

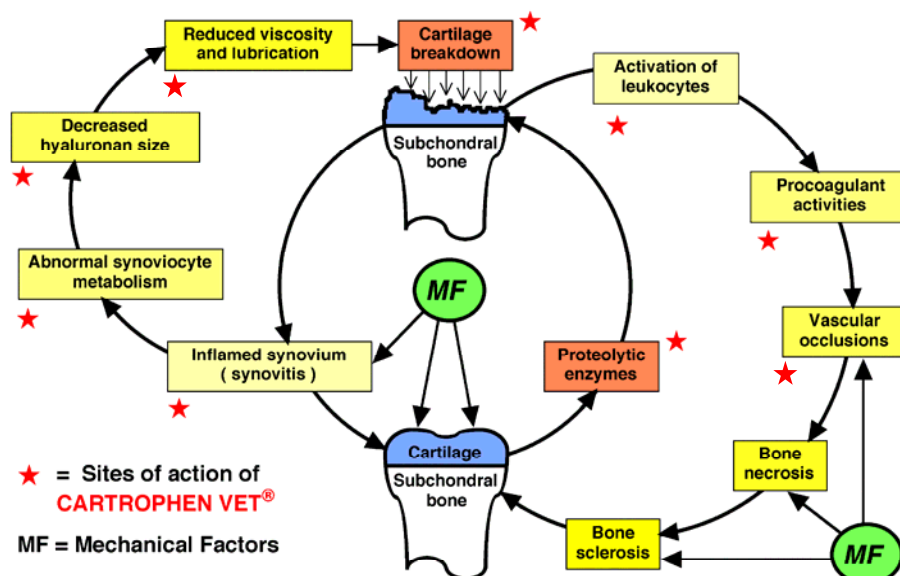
Pain in domestic animals has been defined as an aversive sensory and emotional experience manifesting as an awareness by the animal of damage to or threat of damage to the integrity of its tissues. This results in a change in the animal's physiologic responses and behaviour to reduce or avoid damage, to reduce the likelihood of recurrence and to promote recovery. Anil SS, et al. (2002). *JAVMA*. 220: 313-319.

Pain management is important in the OA treatment, however, the protective and restorative roles played by pain must be acknowledged to avoid compromising the other objectives of the treatment of OA. Therefore, treating the disease rather than the sign(s) of disease (eg. pain) minimises risk of further injury and maximises recovery (eg. with cruciate ligament strain/partial rupture).

CARTROPHEN VET is not an analgesic.

It alleviates the clinical signs of osteoarthritis by acting on the underlying causes of the disease.

Research has shown that CARTROPHEN VET achieves this effect by acting on a number of pathways responsible for the pathogenesis of osteoarthritis

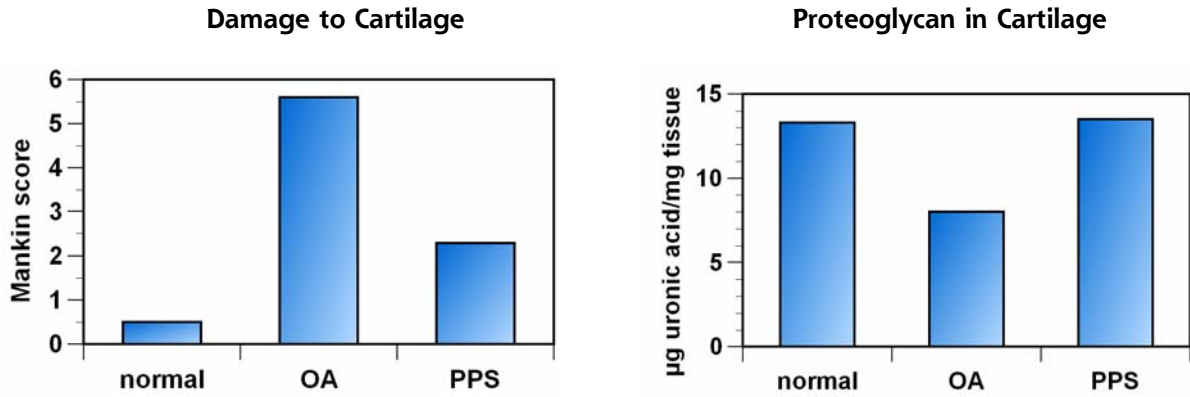


CARTROPHEN VET contains pentosan polysulfate (PPS), a semisynthetic polysulfated polysaccharide that possesses disease modifying and anti-arthritis chondroprotective properties. The PPS in CARTROPHEN VET has been shown to exhibit the following actions:

- Stimulates chondrocytes to synthesize cartilage matrix;
- Stimulates synoviocyte biosynthesis of hyaluronic acid;
- Inhibits and modulates pro-inflammatory mediators, bio-active amines such as: histamine, serotonin, superoxide free radical, enzymes such as elastase, hyaluronidase, cathepsins, TNF- α converting enzyme (TACE) and proteins of the complement system which are implicated in the degradation of cartilage matrix components;
- Mobilizes thrombi and fibrin deposits in synovial tissues and subchondral blood vessels, thus increasing the perfusion of the joint, with resulting improvement in nutrition;
- Mobilizes lipids and cholesterol in synovial and subchondral blood vessels;
- Strong anti-inflammatory properties which act at the cellular and humoral level;
- De-sensitisation of platelets aggregation and clotting;
- Increases the levels of natural inhibitors of metalloproteinases in cartilage;
- Stimulates plasma levels of tissue plasminogen activator and decreases plasminogen activator inhibitor, which improves clot dissolution;
- Increases plasma lipase levels.

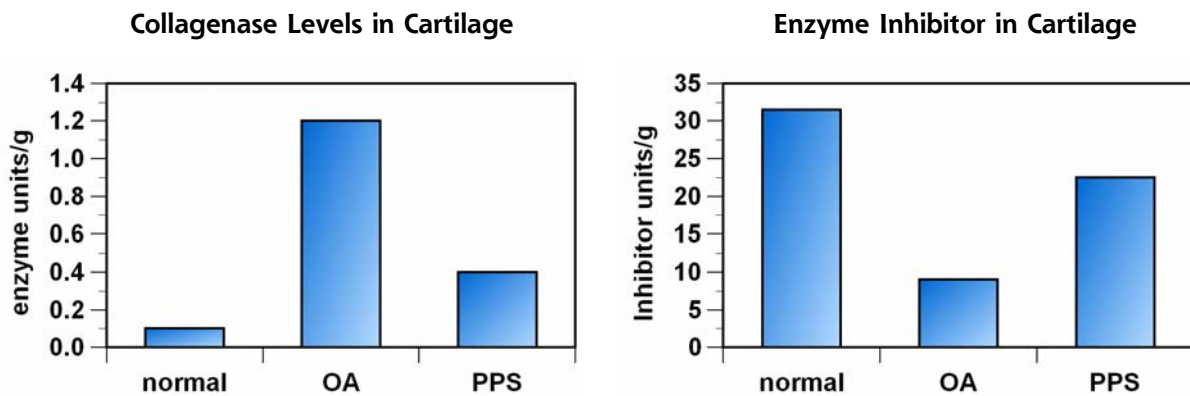
While CARTROPHEN VET will benefit acute through to chronic OA, due to the progressive nature of this disease, early intervention with CARTROPHEN VET in acute injuries that respond clinically as connective tissues regain normal performance is desirable.

CARTROPHEN VET preserves cartilage integrity and function in a canine model of osteoarthritis.



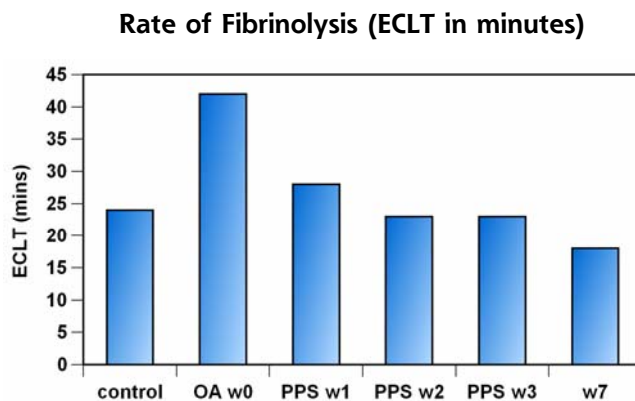
Histopathologic grading of the microscopic severity of cartilage damage (Mankin Score) was significantly reduced. The levels of uronic acid (an index of cartilage proteoglycan content which provides the resilience to cartilage) were elevated to the normal range in cartilage from dogs with transected anterior cruciate ligaments when compared to non-treated OA dogs four weeks after a course of four injections (2mg/kg) of pentosan polysulfate. Rogachefsky RA, et al. (1993). *Osteoarthritis Cart.* 1: 105-114.

CARTROPHEN VET inhibits enzymes implicated in cartilage degradation in osteoarthritis.



Levels of active metalloproteinase (as collagenase) were significantly reduced and tissue inhibitor of metalloproteinase (TIMP) elevated to the normal range in cartilage from dogs with transected anterior cruciate ligaments when compared to non-treated OA dogs four weeks after a course of four injections (2mg/kg) of pentosan polysulfate. Rogachefsky RA, et al. (1993). *Osteoarthritis Cart.* 1: 105-114.

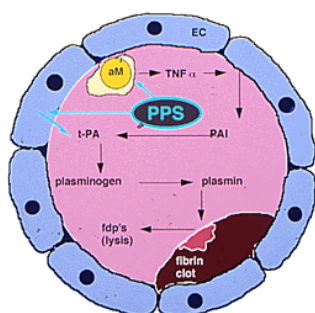
CARTROPHEN VET has a normalizing effect on the fibrinolytic system which is defective in osteoarthritis, thus increasing the perfusion of the joint tissues.



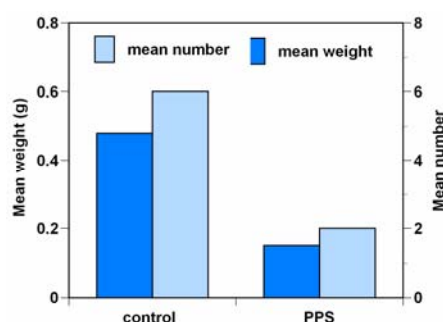
Studies on plasma of OA dogs have demonstrated that they have a reduced capacity to dissolve fibrin clots compared to plasma from non-osteoarthritic dogs. This defect in fibrinolysis, measured as euglobulin clot lysis time (ECLT), contributes to periarticular and subchondral bone thrombosis which can produce pain and osteonecrosis in affected joints. Treatment with four pentosan polysulfate (calcium salt) injections (3mg/kg) at weekly intervals normalized the ECLT in OA dogs. This effect was still evident four weeks after the last injection. Ghosh P and Cheras PA (2001). *Best Pract. Res. Clin. Rheumatol.* 15(5): 693-710.

CARTROPHEN VET promotes breakdown of venous thrombi in the dog which results in improved perfusion of the joint tissues.

Mechanism of Fibrinolysis Regulation



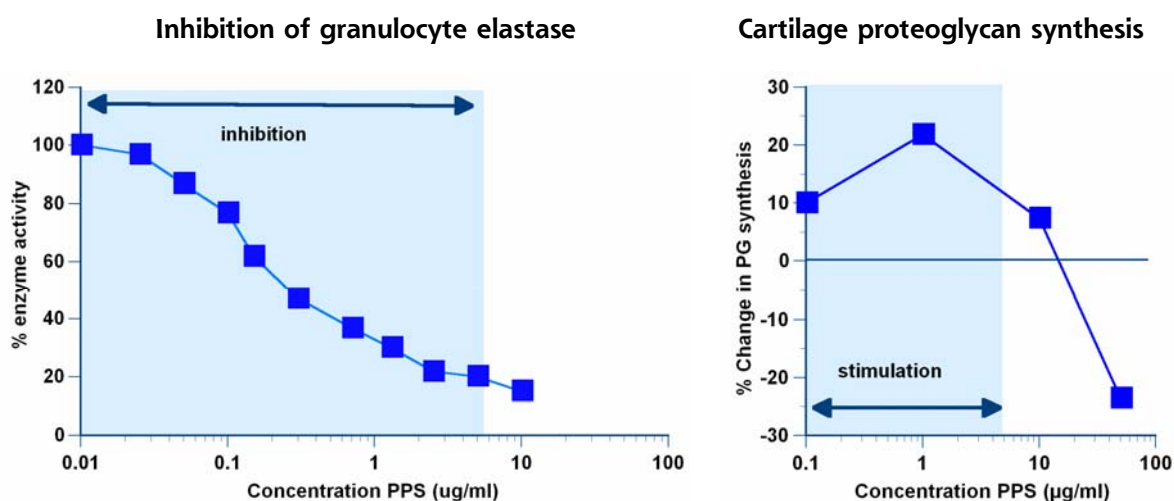
Clot lysis in the Dog after PPS injections



Pentosan polysulfate increases fibrinolysis by stimulating the release of tissue plasminogen activator (t-PA) from endothelial cells (EC). This protein catalyzes the production of plasmin from plasminogen which dissolves fibrin clots (FC) to soluble fibrin degradation product (fdp). In addition, pentosan polysulfate suppresses the release of tumour necrosis factor alpha (TNF- α) from activated monocytes (M), thus decreasing the release of plasminogen activator inhibitor (PAI). Klocking H-P and Markwardt F (1986). *Thromb. Res.* 41: 739-744.

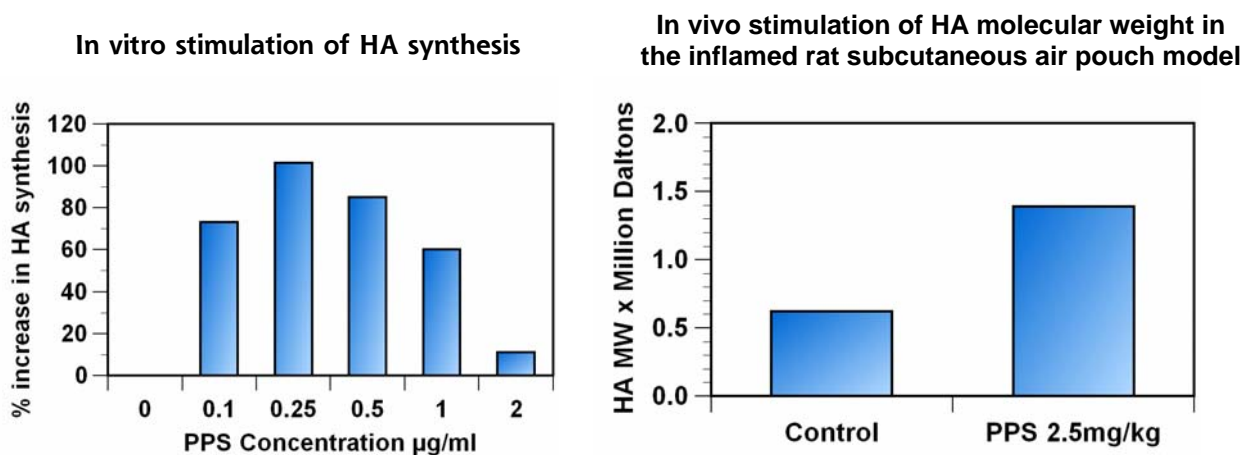
Studies in the dog have confirmed that pentosan polysulfate reduced the average number and average weight of experimental venous thrombi. Fitzgerald DE (1967). *Thromb. Diath. Haem.*, 17: 418-422.

CARTROPHEN VET has an affinity for cartilage resulting in therapeutic concentrations for four days.



Studies using radioactive pentosan polysulfate have indicated that it has an affinity for cartilage with an estimated peak concentration of 4 μ g/g after a 3mg/kg injection and a half-life of fourteen hours. This arises from the strong binding of the drug to cartilage proteins and results in therapeutic drug levels in the cartilage for up to four days after treatment. This level of pentosan polysulfate in the cartilage would be adequate to inhibit enzymes implicated in cartilage degradation (such as elastase) and would stimulate the synthesis of cartilage proteoglycan. Baici A, et al. (1981). *Biochem. Pharmacol.* 30: 703-708; Collier SA and Ghosh P (1989). *Ann. Rheum. Dis.* 48: 372-381.

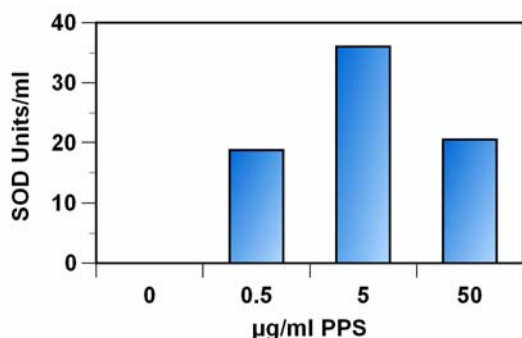
CARTROPHEN VET improves the viscosity of synovial fluid.



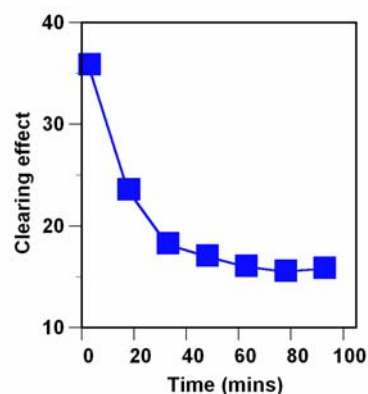
Hyaluronic acid (HA) confers to synovial fluid its unique viscoelastic properties which provide exceptional lubrication and weight bearing characteristics. In OA, the synthesis of HA by synovial fibroblasts is abnormal and the molecular weight (MW) of HA may be decreased. This results in compromised ability of the OA joint to dissipate the compressive and shearing forces required for normal joint movement and function. At concentrations achieved by pentosan polysulfate in synovial fluid after normal therapeutic doses, an anabolic effect on OA synovial fibroblasts results and synthesis of HA is increased, restoring the molecular and physical characteristics of synovial fluid which are essential for normal joint function. Hutadilok N, et al. (1988). *Curr. Ther. Res.* 4: 845-860; Francis D, et al. (1993). *Rheum. Int.* 13: 61-64.

CARTROPHEN VET stimulates the release of the free radical scavenging enzyme superoxide dismutase and lipase.

SOD from Endothelial Cells



Clearing effect on Plasma Lipids

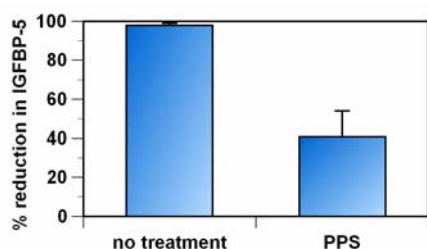


Pentosan polysulfate, when studied on cultured human umbilical endothelial cells, stimulated superoxide dismutase (SOD) production suggesting pentosan polysulfate protects connective tissue against free radicals generated in the OA joint, therefore preserving normal joint function. Bowman L, et al. (1994). *Int. Soc. Free Radical Res., 7th Biennial Meeting 1994*.

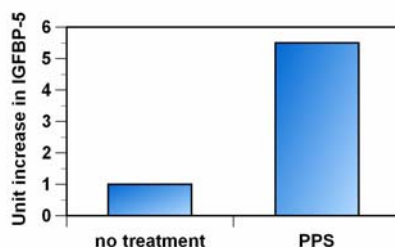
From histopathological examination of joint tissues, accumulation of lipid in microcapillaries as well as the synovial space are implicated in the cause of vascular congestion in OA joints. Studies in the rat and dog of pentosan polysulfate (3mg/kg and 25mg/kg respectively) demonstrated clearing of plasma lipids due to the release of plasma lipase, thus improving joint perfusion. Brunaud M, et al. (1967). *Progr. Biochem. Pharmacol.* 3: 393-402.

CARTROPHEN VET stimulates the production of insulin-like growth factor-1 which is essential for healthy cartilage.

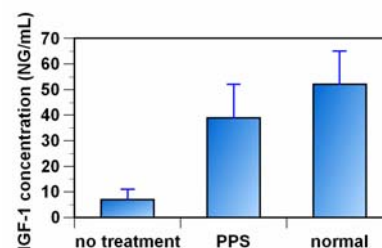
PPS inhibits proteolysis of IGFBP-5 by decreasing complement C1s activation by C1r.



PPS increases IGFBP-5 concentration.



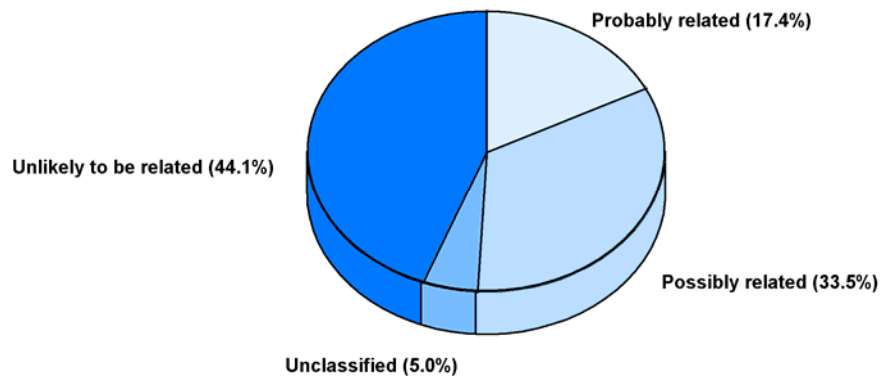
PPS increases synovial fluid IGF-1 concentration.



Insulin-like growth factor-1 (IGF-1) is an essential trophic factor for healthy cartilage, stimulating the incorporation of sulfate and encouraging cartilage growth. Pentosan polysulfate increases IGF-1 production by inhibiting complement C1s, an enzyme which degrades insulin-like growth factor binding protein (IGFBP-5). IGFBP-5 stabilises and potentiates IGF-1. Pentosan polysulfate also increases IGF-1 levels in synovial fluid. Clemmons DR, et al. (2002). *Arthritis Rheum.* 46(3): 694-703.

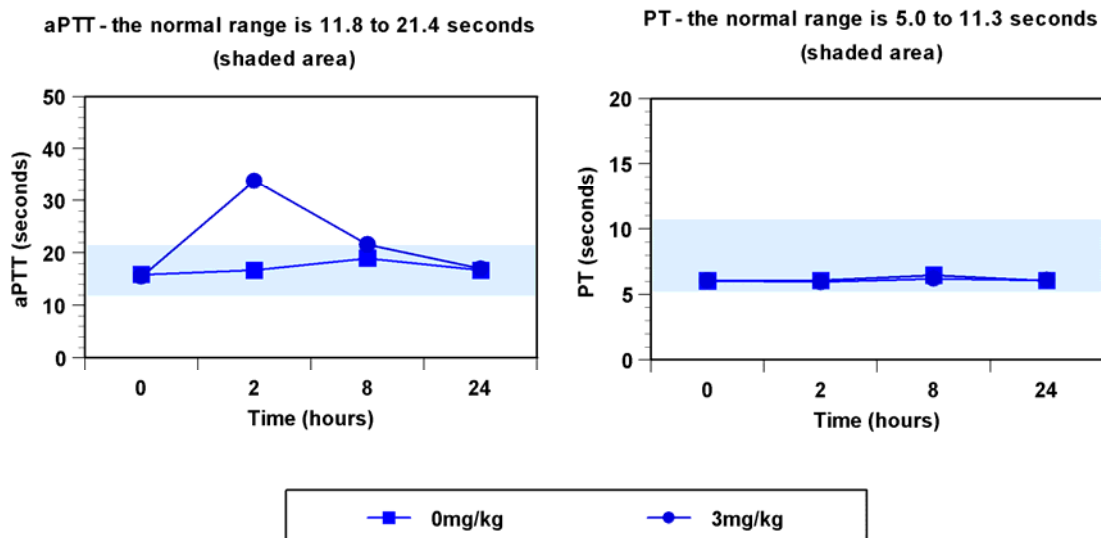
CARTROPHEN VET is safe.

Relationship of suspected adverse reactions to CARTROPHEN VET



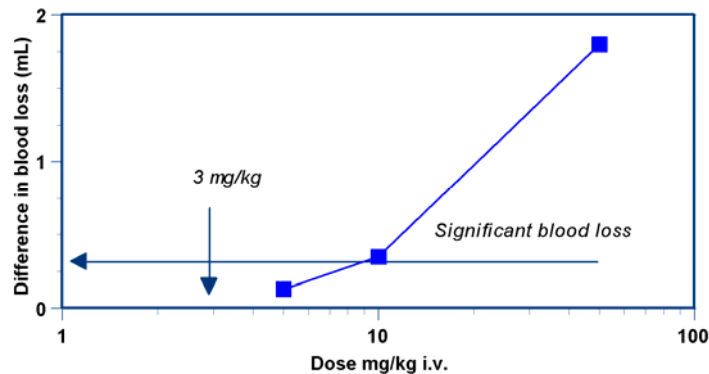
CARTROPHEN VET has a low incidence of side effects that are mild and transitory. The estimated real incidence of suspected adverse reactions probably and possibly associated with CARTROPHEN VET in the United Kingdom was 0.074% on an individual dose basis (submissions to the Veterinary Medicines Directorate from 1991 to 1999; assumes 10% of reactions reported). Vomiting (onset 5 to 15 minutes after administration) and general demeanour changes (quietness and/or lethargy and/or inappetence) for 1 or 2 days after administration were considered product related. While the cause of these reactions is presently unknown, there was some evidence that a transitory elevation in histamine activity may be implicated. Anti-histamine medication was proposed as a rational treatment in these cases. There was no evidence of spontaneous bleeding (local or systemic) attributable to CARTROPHEN VET such as that observed with heparin. Hannon RL, et al. (2003). *J. Small. Anim. Pract.* 44(5): 202-208.

CARTROPHEN VET has temporary effects on blood.



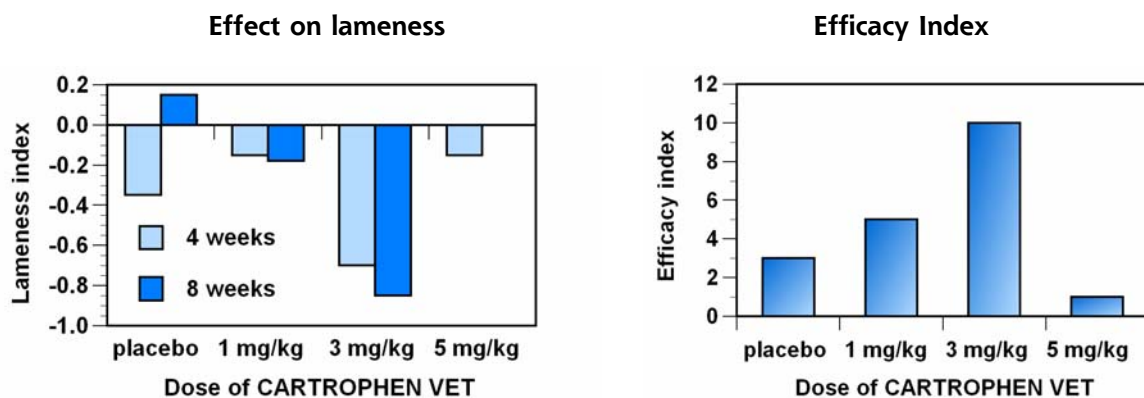
Investigations in the dog of the blood clotting parameters activated partial thromboplastin time (aPTT) and prothrombin time (PT) following s.c. administration of 3mg/kg CARTROPHEN VET on twelve occasions at weekly intervals showed aPTT increased 2 hours following administration but returned to near normal at 8 hours and PT remained within the normal range. Substance-related local intolerance reactions (eg. haematoma) and evidence of systemic bleeding (eg. ecchymosis or gastrointestinal bleeding) were not observed, even at doses up to and including 30mg/kg applied for twelve weeks (10x the recommended dose and 3x times the normal treatment duration). With this drug's pharmacological profile, bleeding would not be expected in an animal with normal haemostasis and CARTROPHEN VET presents a low risk despite temporary effects on some clotting parameters. Data on file, Biopharm Australia Pty Ltd.

CARTROPHEN VET does not have a global effect on the coagulation system.



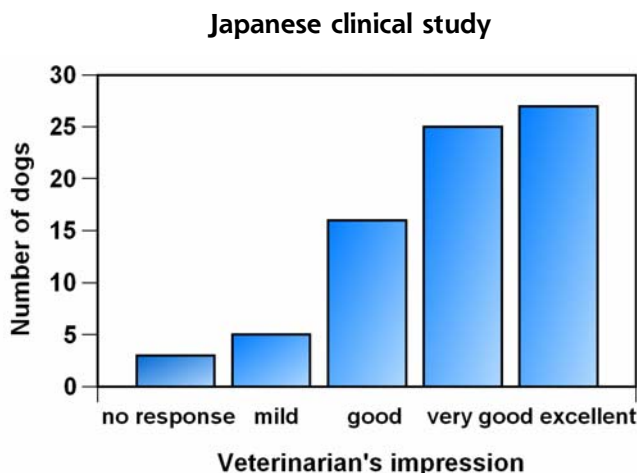
Following i.v. bolus injection of pentosan polysulfate in the rabbit ear bleeding model, a minimal but significant haemorrhagic effect was observed at 3x the recommended dose of CARTROPHEN VET. Pentosan polysulfate in humans and laboratory animals shows a mild anticoagulant effect, which is between one sixth to one tenth of the potency of heparin. However, pentosan polysulfate is a potent activator of the fibrinolytic system since it stimulates the release of tissue plasminogen activator from the endothelium. The net result of pentosan polysulfate on these activities is the dissolution of thrombotic emboli in blood vessels without a pronounced anticoagulant effect. Thus pentosan polysulfate, unlike heparin, does not exhibit a global alteration of the blood clotting system. Maffrand J-P, et al. (1991). *Semin Thromb Hemost* 17(Suppl 2): 186-198.

CARTROPHEN VET has an optimal clinical efficacy in dogs at 3mg/kg s.c. on four occasions at weekly intervals. Higher dose had a decrease in clinical effect which was not a toxic effect.



Dose response studies in OA dogs have demonstrated that 3mg/kg of CARTROPHEN VET was optimal and both 1mg/kg and 5mg/kg were not as effective. The lameness index was measured on a 5 point scale of severity (from "no lameness" to "will not use") and showed a decrease after the four weekly injections which was maintained four weeks after treatment (eighth week). The efficacy index was the number of significant changes in clinical status in each group when compared to base line values. It is proposed that pentosan polysulfate may at high doses have an effect of releasing excessive amounts of inflammatory degradation products and thus at high doses, the anti-inflammatory effect may be sub-optimal. Read RA, et al. (1996). *J. Small Anim. Pract.* 37: 108-114.

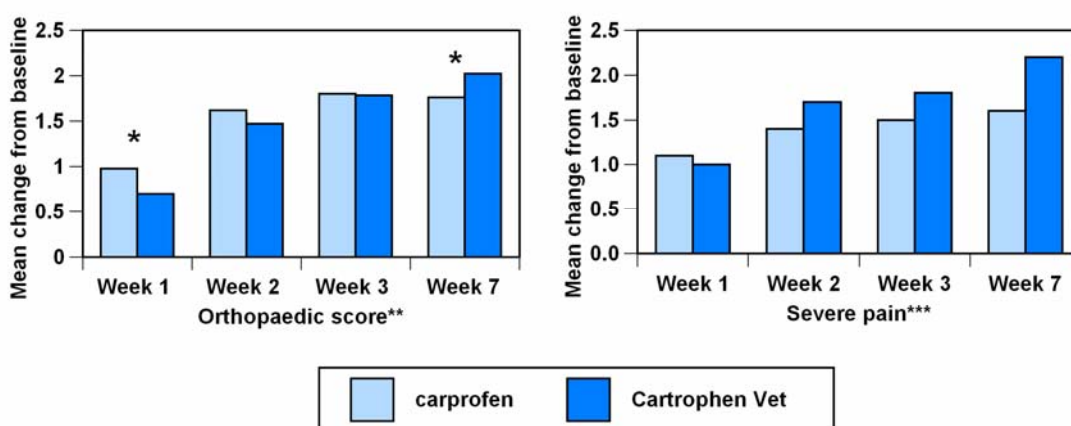
CARTROPHEN VET is effective in reducing the clinical signs of canine osteoarthritis.



The ability of CARTROPHEN VET to address the clinical signs of canine OA, including lameness and pain, has been demonstrated in an open clinical trial in Japan. According to the veterinarian's impression, 96% of cases improved with CARTROPHEN VET treatment, while lameness improved in 84.2% of cases and pain improved in 76.3% of cases. Data on file, Biopharm Australia Pty Ltd.

When it comes to osteoarthritic joint pain and lameness, CARTROPHEN VET is equal or superior to the potent analgesic and anti-inflammatory, carprofen.

German comparator clinical study



* Significant at p < 0.05.

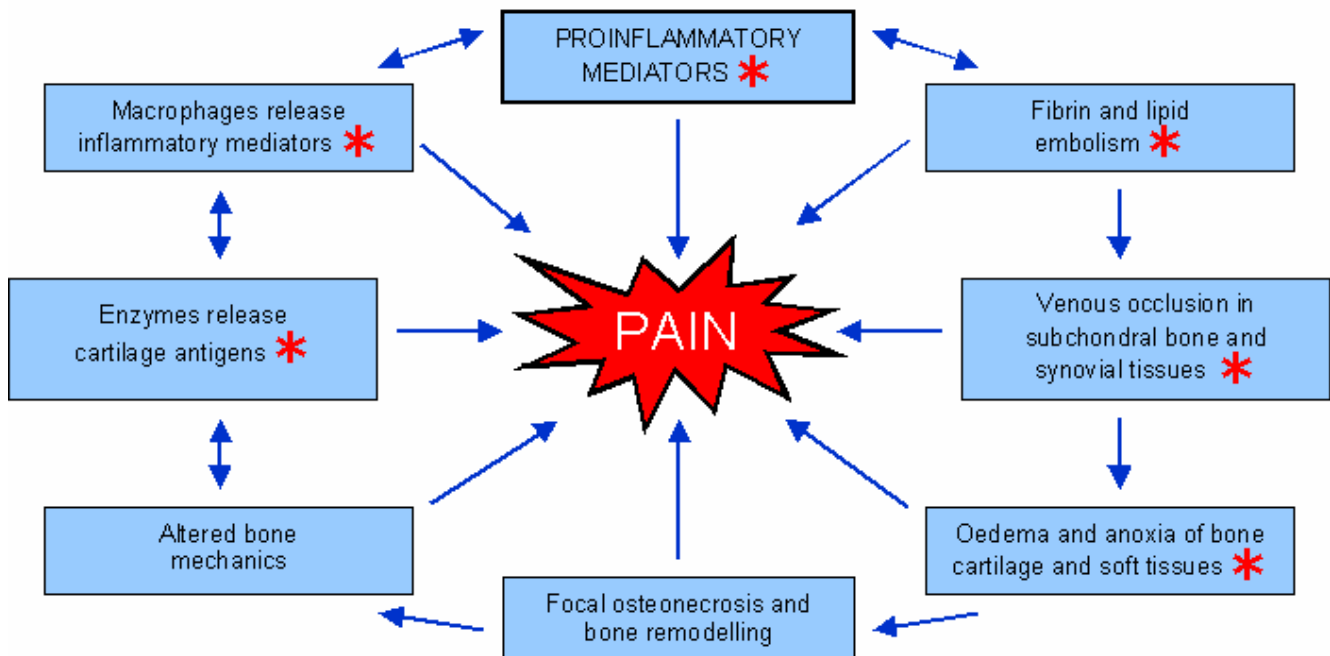
** Orthopaedic score equals the sum of pain and lameness scores

*** Severe pain defined as "vocalising" or "wincing and withdrawing" upon manipulation of the affected limb.

CARTROPHEN VET treatment results in potent effects on pain and lameness in clinical trials that are equal or superior to that of carprofen. This is the first time a disease modifying osteoarthritis drug (DMOAD) has been proven to offer significant pain relief comparable to that afforded by NSAIDs. CARTROPHEN VET has a slightly slower onset of ameliorating effects but longer persistence of these after the recommended four week course of treatment. Smith JG, et al. (2001). *Osteoarthritis Cart.* 9 (Suppl B): S21-S22.

Action of CARTROPHEN VET on biochemical origins of pain.

(* Sites of CARTROPHEN VET action)



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