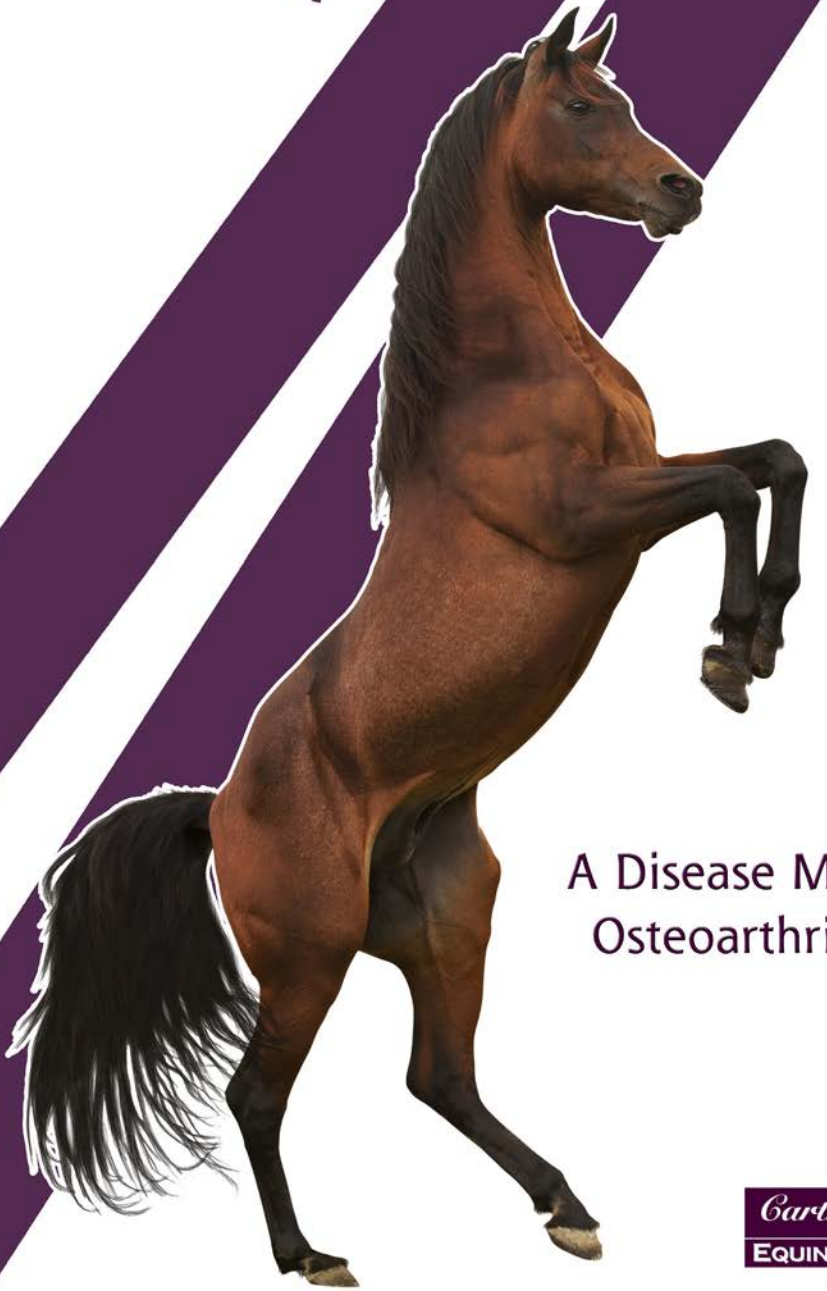
# CARTROPHEN EQUINE FORTE



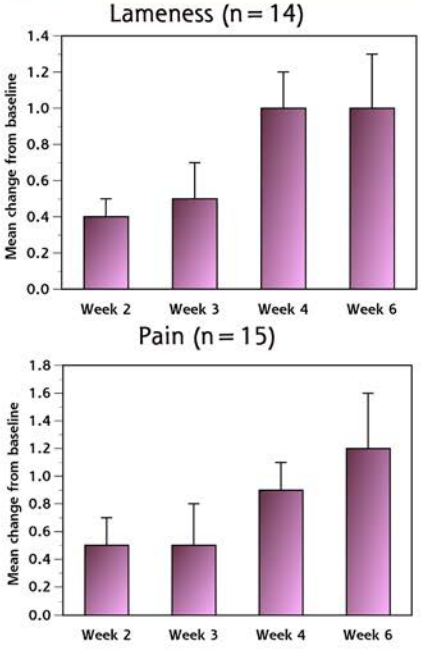
## A Disease Modifying Osteoarthritis Drug

Cartrophen
EQUINE FORTE

CARTROPHEN EQUINE FORTE (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 EQUINE FORTE has therefore been classified as a disease modifying osteoarthritis drug (DMOAD) and represents the rational approach to the medical treatment of osteoarthritis in horses.

# Content

## CARTROPHEN EQUINE FORTE effectively treats lameness and pain in the horse



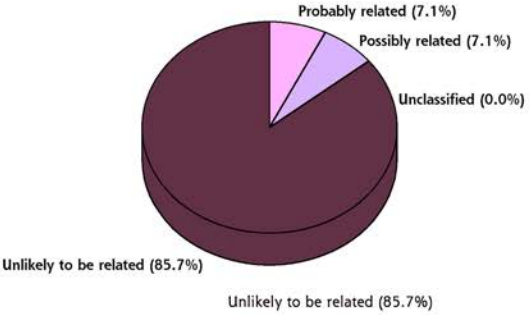

Clinical trial data shows that horses administered Cartrophen once a week for 4 weeks at an average dose of 2.2mg/kg had improved lameness and pain scores during treatment (Weeks 2, 3 and 4) and two weeks after treatment (Week 6). According to the veterinarian's and owner's impression of treatment, at least 60% of cases responded positively to the treatment. *Data on file, Biopharm Australia Pty Ltd.*

## CARTROPHEN EQUINE FORTE is safe in the horse.

Over a 14 year period to August 2007 in Australia, four suspected adverse drug reaction reports involving 14 horses receiving Biopharm Australia pentosan polysulfate (PPS) as Cartrophen Vet have been received. This represents a very low estimated incidence of adverse events on an individual dose basis in the horse of less than 0.01%.

Three of the four reports involved injection site reactions in 13 horses. All were associated with non-veterinarian intramuscular administration, although in one report the use of competitor pentosan polysulfate could not be excluded. The fourth report involved dypsnoea, ataxia and collapse resulting in the death of one horse immediately following the third injection. The product was administered by a non-veterinarian and test results indicated the problem was not anaphylactic in nature but probably related to maladministration of the product by intravenous injection. *Data on file, Biopharm Australia Pty Ltd.*

**Relationship of suspected adverse reaction to Biopharm Australia PPS in the horse**



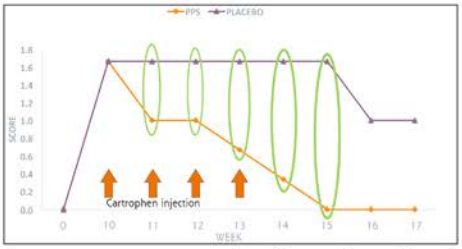
## Evidence of the therapeutic effects of CARTROPHEN in osteoarthritis of equidae.

### A new arthritis model in the donkey

Particles found in naturally occuring osteoarthritis (OA) synovial fluid causes physical and biochemical trauma to the joint, initiating and promoting cartilage damage.

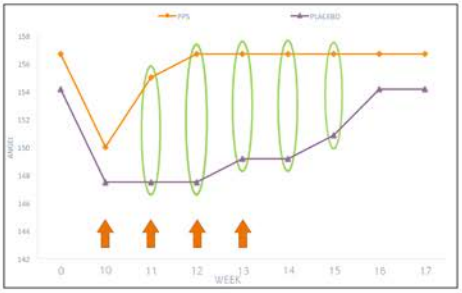
Twelve donkeys were administered heterologous cartilage particles intra-articulary at a dose and schedule proven to produce cartilage damage similar to that observed in horse OA.

### Lameness Score



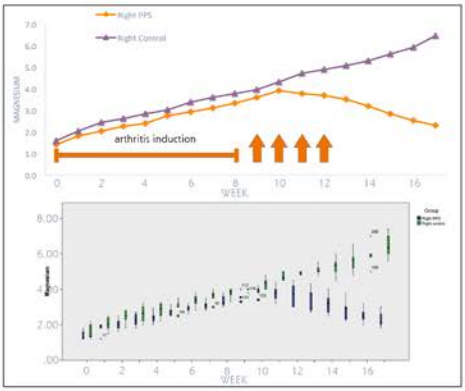

Lameness score was significantely reduced compared to placebo and back to base line after 4 weekly injections of Cartrophen.

### Joint Flexion Angle




Joint flexion also returned to normal after 4 weekly injections of Cartrophen. These changes were supported by improved microscopic and electron microscopy findings.

### Synovial Fluid Magnesium

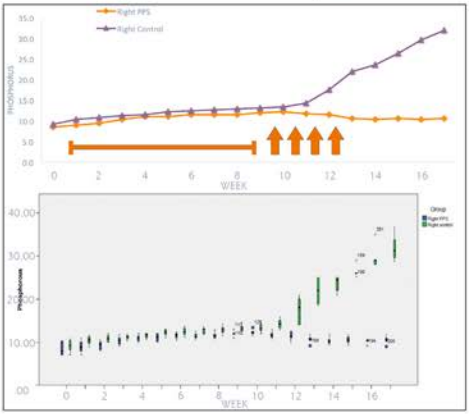



Synovial fluid magnesium salt levels gradually increased during and after arthritis induction in the placebo group, indicating progressive release of magnesium, which is concentrated at the cartilage surface beneath the surface laminar (SL).

This indicates an increasing area of surface damage of the semipermeable SL. Treatment of 4 injections of PPS at 7 day intervals resulted in a return to normal.



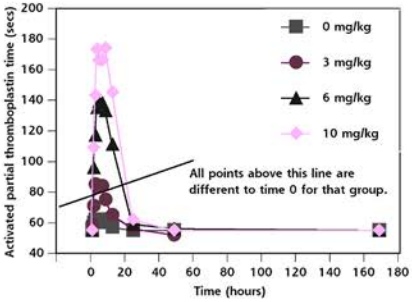
### Synovial Fluid Phosphorus




Elevation of synovial fluid phosphorus correlates with the onset of deeper damage, associated with cartilage fissures and full depth lesions. PPS prevented this change.

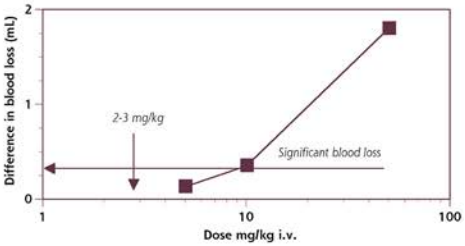
**Conclusion:** Four injections of Cartrophen resulted in significant clinical and biochemical improvement in a new arthritis model.

## CARTROPHEN EQUINE FORTE has temporary effects on blood in the horse.




The safety of Biopharm Australia pentosan polysulfate as Cartrophen Vet in the horse at 3mg/kg, 6mg/kg and 10mg/kg by intramuscular injection has been demonstrated in a university study. Activated partial thromboplastin time (PTT) increased with increasing dose of pentosan polysulfate reflecting an effect on the intrinsic clotting pathway. The researchers noted that at the recommended dose rate for joint problems in the horse (2 to 3mg/kg), PTTs increased within 1 hour of injection, remained significantly elevated for 4 to 5 hours and did not return to baseline times until 24 hours after injection. There was no effect of pentosan polysulfate on prothrombin time confirming no effect on the extrinsic pathway. The researchers considered it logical to recommend that doses up to 3mg/kg should not be administered within 24 hours of high stress activities or where physical injury may occur and to avoid concurrent treatment with anticoagulant drugs. *Dart AJ, et al. (2001) Aust. Vet. J. 79(3):624-627.*

## CARTROPHEN EQUINE FORTE 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 3-5x the recommended dose of CARTROPHEN EQUINE FORTE. 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.*

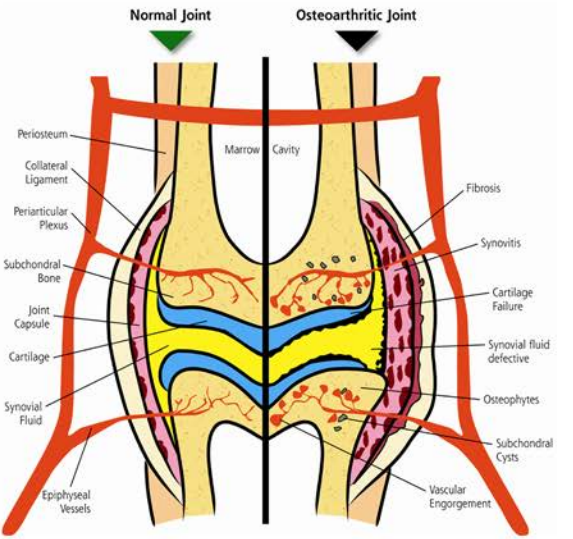
## The degenerative effects of osteoarthritis on the joint

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 the 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. NorthAm: Sm. Anim. Pract. 30: 933-949.*



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).

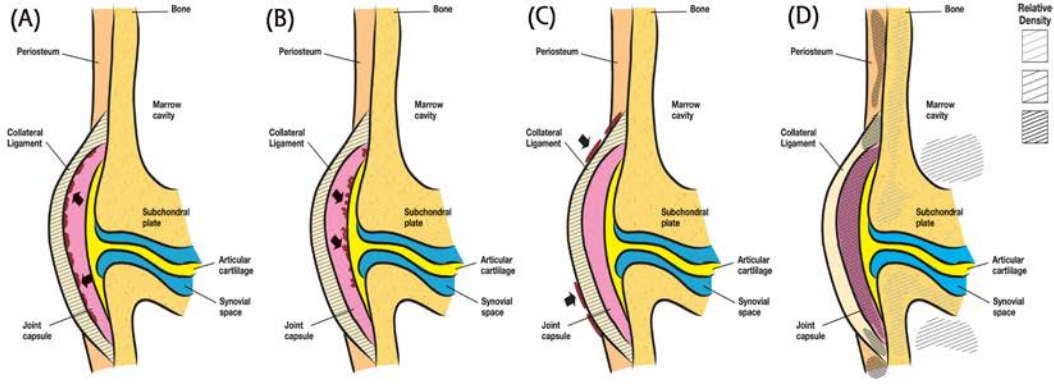
### Schematic representation of the location and distribution of articular nerve endings

*[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.

## CARTROPHEN EQUINE FORTE is not an analgesic.

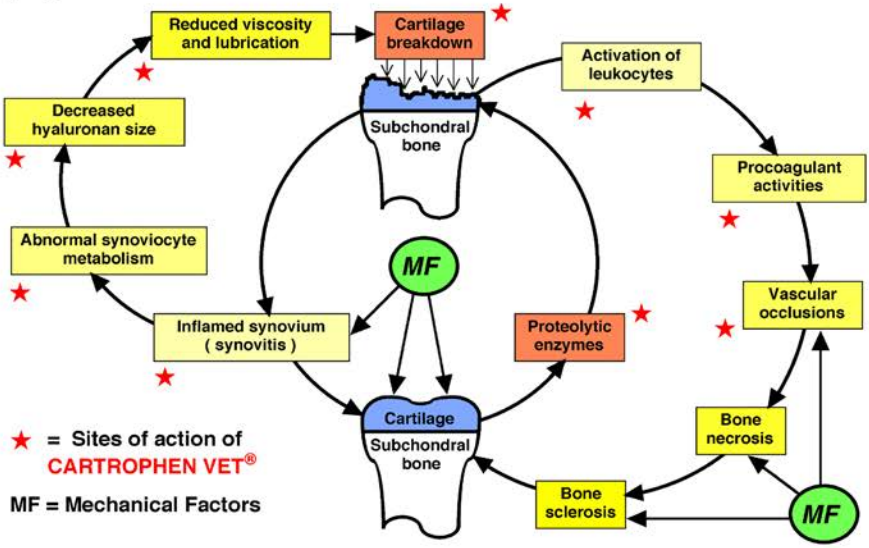
**It alleviates the clinical signs of osteoarthritis by acting on the underlying causes of the disease.**

**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-arthritic chondroprotective properties. The PPS in CARTROPHEN VET has been shown to exhibit the following actions:

(a) Stimulates chondrocytes to synthesize cartilage matrix;
(b) Stimulates synoviocyte biosynthesis of hyaluronic acid;
(c) 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;
(d) Mobilizes thrombi and fibrin deposits in synovial tissues and subchondral blood vessels, thus increasing the perfusion of the joint, with resulting improvement in nutrition;
(e) Mobilizes lipids and cholesterol in synovial and subchondral blood vessels;



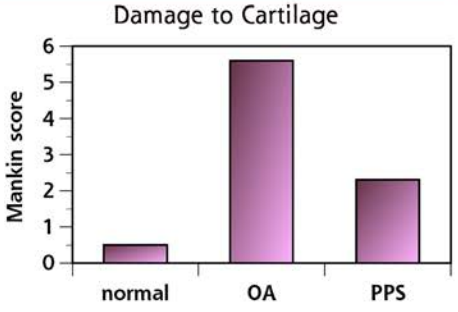


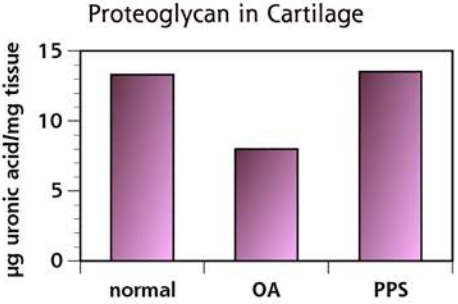
(f) Strong anti-inflammatory properties which act at the cellular and humoral level;
(g) De-sensitisation of platelets aggregation and clotting;
(h) Increases the levels of natural inhibitors of metalloproteinases in cartilage;
(i) Stimulates plasma levels of tissue plasminogen activator and decreases plasminogen activator inhibitor, which improves clot dissolution;
(j) 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 EQUINE FORTE preserves cartilage integrity and function in a canine model of osteoarthritis.

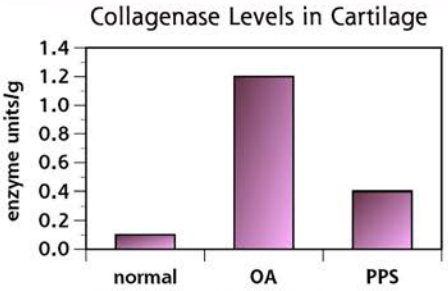


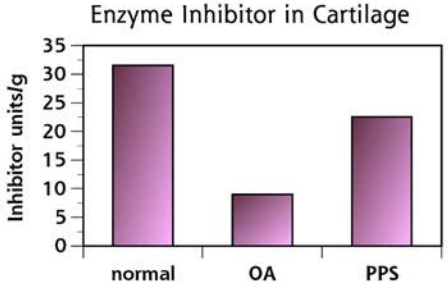



Histopathologic grading of the microscopic severity of cartilage damage (Mankin Score) was significantly reduced. The levels of uronic acid (an index of cartilage proteoglycan content which provides the resilience to cartilage) were elevated to the normal range in cartilage from dogs with transected 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 EQUINE FORTE inhibits enzymes implicated in cartilage degradation in OA.

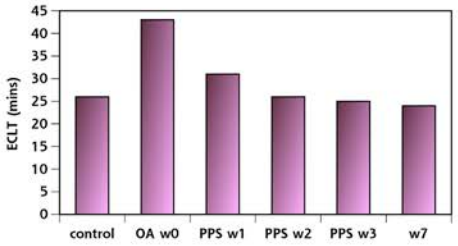



Levels of active metalloproteinase (as collagenase) were significantly reduced and tissue inhibitor of metalloproteinase (TIMP) elevated to the normal range in cartilage from dogs with transected anterior cruciate ligaments when compared to non-treated OA dogs four weeks after a course of four injections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

CARTROPHEN EQUINE FORTE has normalizing effect on the fibrinolytic system which is defective in OA, thus increasing the perfusion of the joint tissues.

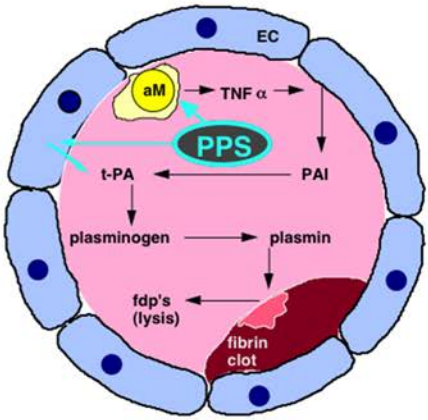
Rate of Fibrinolysis (ECLT in minutes)



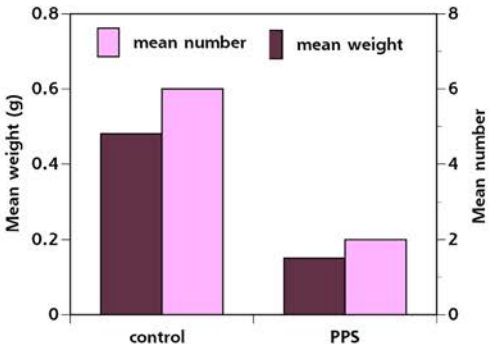

Studies on plasma of OA dogs have demonstrated that they have a reduced capacity to dissolve fibrin clots compared to plasma from non-osteoarthritic dogs. This defect in fibrinolysis, measured as euglobulin clot lysis time (ECLT), contributes to periarticular and subchondral bone thrombosis which can 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 EQUINE FORTE promotes breakdown of venous thrombi which results in improved perfusion of the joint tissues.

Mechanism of Fibrinolysis Regulation




Clot lysis in the Dog after PPS injection

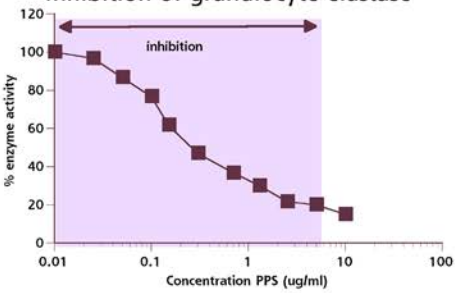



Pentosan polysulfate increases fibrinolysis by stimulating the release of tissue plasminogen activator (t-PA) from endothelial cells (EC). This protein catalyzes the production of plasmin from plasminogen which dissolves fibrin clots (FC) to soluble fibrin degradation product (fdp). In addition, pentosan 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.*

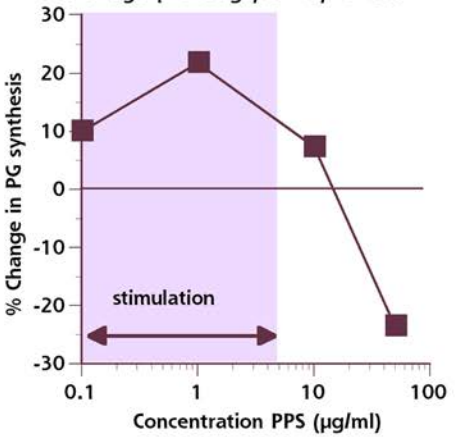
Studies in the dog have confirmed that pentosan polysulfate reduced the average number and average weight of experimental venous thrombi. *Fitzgerald DE (1967). Thromb. Diath. Haem., 17: 418-422.*

**CARTROPHEN EQUINE FORTE has an affinity for cartilage resulting in therapeutic concentrations for four days.**

Inhibition of granulocyte elastase




Cartilage proteoglyca synthesis

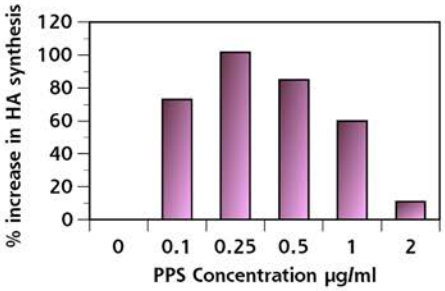



Studies using radioactive pentosan polysulfate have indicated that it has an affinity for cartilage with an estimated peak concentration of 4µg/g after a 3mg/kg injection and a half-life of fourteen hours. This arises from the strong binding of the drug to cartilage proteins and results in therapeutic drug levels in the cartilage for up to four days after treatment.

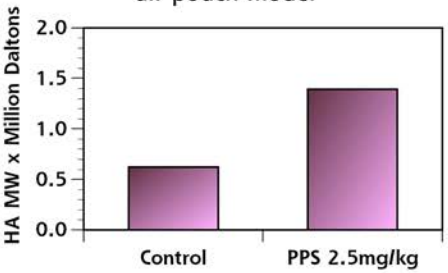
This level of pentosan polysulfate in the cartilage would be adequate to inhibit enzymes implicated in cartilage degradation (such as elastase) and would stimulate the synthesis of cartilage proteoglycan. *Baici A, et al. (1981). Biochem. Pharmacol. 30: 703-708; Collier SA and Ghosh P (1989). Ann. Rheum. Dis. 48: 372-381.*

**CARTROPHEN EQUINE FORTE improves viscosity of synovial fluid.**

In vitro stimulation of HA synthesis



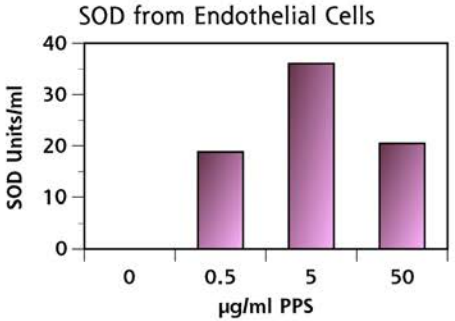

In vivo stimulation of HA molecular weight in the inflamed rat subcutaneous air pouch model

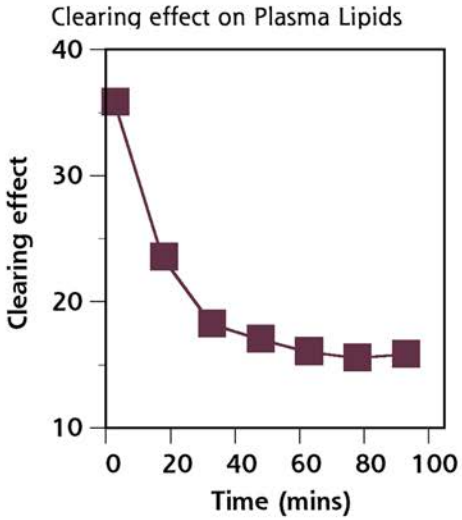



Pentosan polysulfate, when studied on cultured human umbilical endothelial cells, stimulated superoxide dismutase (SOD) production suggesting pentosan polysulfate protects connective tissue against free radicals generated in the OA joint, therefore preserving normal joint function. *Bowman L, et al. (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 EQUINE FORTE stimulates the release of the free radical scavenging enzyme superoxide dismutase and lipase.

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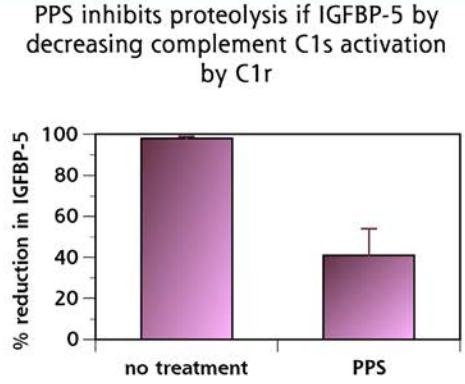
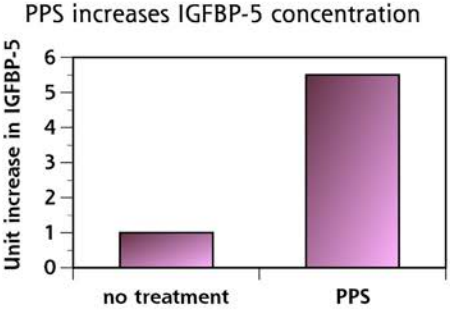
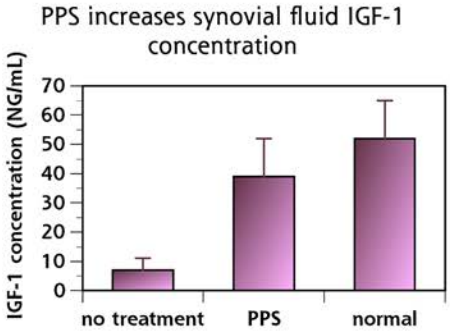
CARTROPHEN EQUINE FORTE stimulates the production of insulin-like growth factor-1 which is essential for healthy cartilage





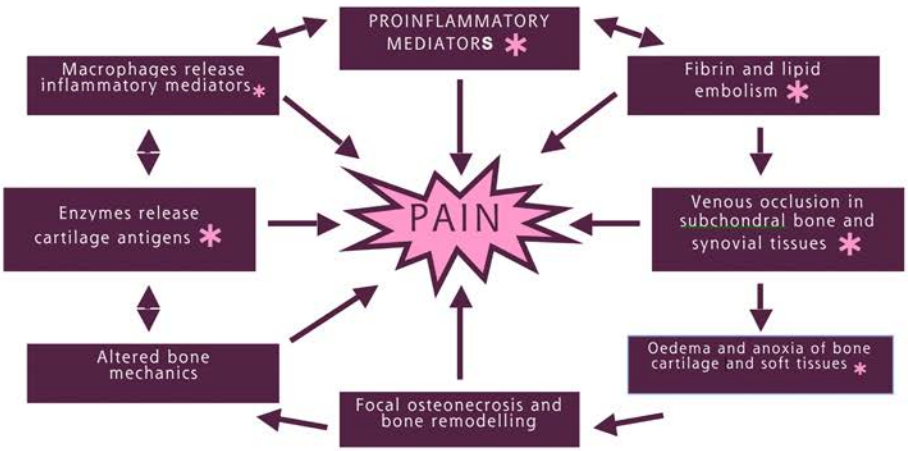




Insulin-like growth factor-1 (IGF-1) is an essential trophic factor for healthy cartilage, stimulating the incorporation of sulfate and encouraging cartilage growth. Pentosan polysulfate increases IGF-1 production by inhibiting complement C1s, an enzyme which degrades insulin-like growth factor binding 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.*



## Action of CARTROPHEN EQUINE FORTE on biochemical origins of pain

( * Sites of CARTROPHEN EQUINE FORTE action)



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