



SYNOVIUM®AGILITY

Objective

The objective of this document is to provide detailed information about SYNOVIUM®AGILITY a product specifically designed for the maintenance and improvement of joint health. This document summarizes the current essential research behind SYNOVIUM®AGILITY including several animal clinical studies and demonstrates the beneficial effects of SYNOVIUM®AGILITY in the treatment of osteoarthritis (OA) in dogs and horses. Moreover, it provides a short overview on the pathogenesis of osteoarthritis (OA) in animals.

Product definition, compliance and safety

SYNOVIUM®AGILITY consists of Bioactive Collagen Peptides (BCP®), which are specific, highly purified hydrolyzed collagen peptides with neutral taste and odor. The average molecular weight is approx. 6.0 kDa. They are suitable for protein enrichment in pet food applications such as treats or complete pet foods (wet and dry).

The product is in compliance with Regulation (EC) No. 852/2004 on the hygiene of foodstuffs, Regulation (EC) No. 853/2004 and Regulation (EC) No. 999/2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies, including amendments regarding country classification and specified risk material.

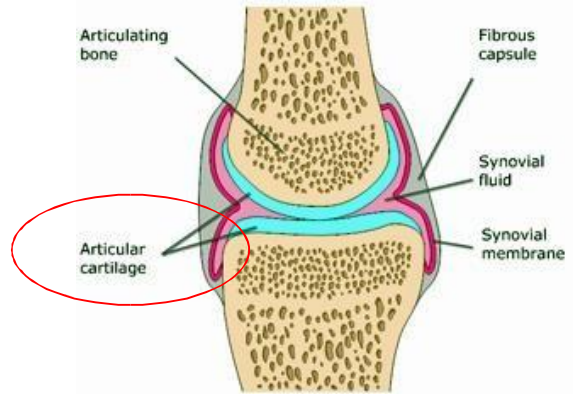
A number of international bodies have expressed opinions with regard to the safety of Bioactive Collagen Peptides (BCP®).

BCPs® are food and non-food additives, and therefore carry no E-number. The Swedish National Veterinary Institute (SVA) have performed virus risk assessments and demonstrated that BCPs are safe. In the United States of America BCP® have been granted "Generally Recognized as Safe (GRAS)" status by the FDA (Docket Number 77N-0232).

Background information on osteoarthritis (OA):

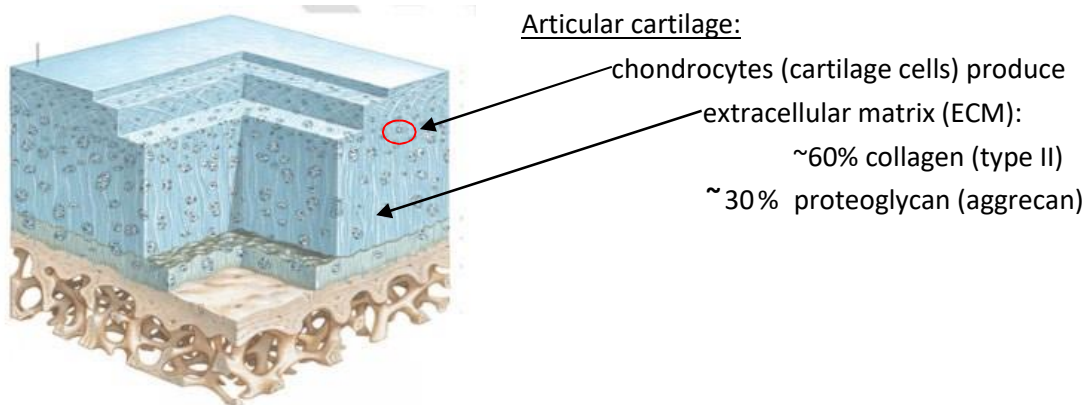
Anatomy

A joint connects two or more bones. Most joints in the body are mobile, allowing the bones to move in relationship to each other. Joints are held together by the joint capsule. The thin inner lining of the joint capsule is the synovial membrane which produces synovia fluid to lubricate the joint. The ends of the bones are covered by a smooth layer of articular cartilage.



(Barron 2013)

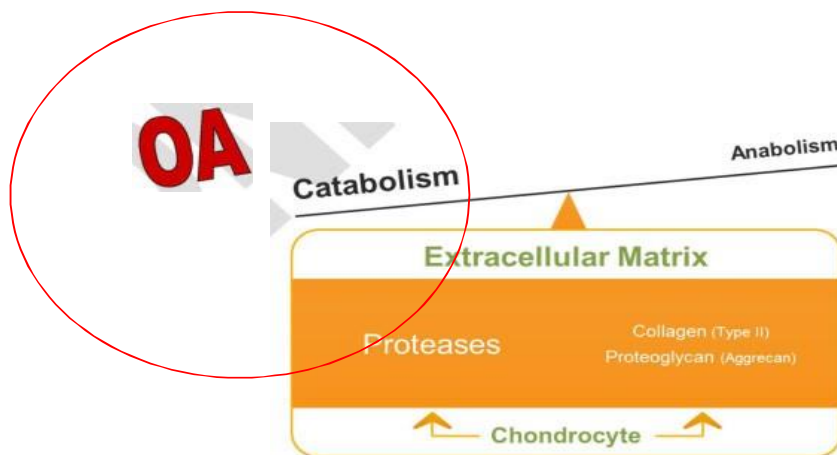
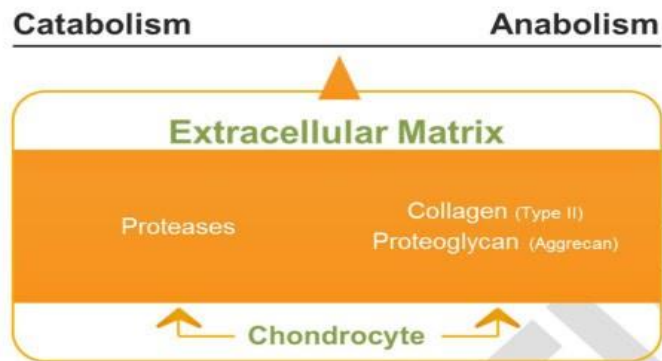
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Cartilage does not contain blood vessels. The chondrocytes are supplied by diffusion; therefore, cartilage grows and repairs more slowly. The chondrocytes are responsible for the anabolic and catabolic balance of the cartilage metabolism.

Background information on osteoarthritis (OA): Pathogenesis



Osteoarthritis (OA) is a degenerative joint disease characterized by progressive destruction of normal articular cartilage and sub-chondral bone (Martinek 2003). It is typically manifested by pain and lameness.

The chondrocytes play a central role in the development of osteoarthritis (OA) because they are responsible for the anabolic and catabolic balance of the cartilage metabolism. If the balance between catabolism and anabolism is disturbed, then degenerative joint disease might develop (Gelse et al. 2003; Bello & Oesser 2006). In the degenerative process, chondrocytes fail to sufficiently produce extracellular matrix (ECM) and progressive cartilage destruction starts (Buckwalter & Mankin 1998). When the cartilage cells become damaged, they release increased amounts of proteases (including metalloproteinases) and cytokines, which further destroy the structure of the ECM (Fernandes et al. 2002).

The loss of articular cartilage is the most critical point in OA; subsequently, it comes to bone deformation, synovitis, shrinking joint capsule and muscular atrophy. The cardinal symptoms of osteoarthritis are pain and lameness (Veje et al. 2002).

Horses are also affected by osteoarthritis (OA) with a high incidence. More than 60% of equine lameness is based on OA (Caron & Genovese 2003). OA can occur early in sports horses or later in aging horses. Risk factors can be abnormal physical stress levels, joint congruence changes, fractures and micro-fractures in sub-chondral bone. The metacarpophalangeal (MCP) joint is the most common joint for spontaneous OA in racehorses, followed by the carpal joints. Both joints have



close-fitting articular surfaces that can quickly develop linear erosions and wear lines in association with osteochondral fragmentation (McIlwraith et al. 2012).

Treatment of osteoarthritis (OA)

There is still no cure for osteoarthritis (OA) today. The goals of an optimal OA treatment are to improve quality of life by minimizing pain and discomfort and in addition to slow down the progression of joint degeneration. OA treatment should also include a combination of analgesics, regular monitoring of body weight and moderate daily physical activity (Marshall et al. 2009).

Symptomatic treatment

It is important to treat pain because it is the main symptom of osteoarthritis. Non-steroidal anti-inflammatory drugs (NSAIDs) are often the first drugs used by veterinarians. Traditional NSAIDs reduce pain by inhibiting particular enzymes such as cyclooxygenases COX1/2. These enzymes interfere with the body's production of inflammatory molecules, which are responsible for pain and swelling (Löscher et al 1999).

Animals subjected to pain management must be monitored by re-examination and laboratory testing at prescribed intervals in order to assess the efficacy of NSAIDs. Drug metabolism varies among species, breeds, and individuals and adverse health effects cannot be excluded. Liver, kidney or gastric damage can occur, in particular in geriatric patients. Pain relief in cats can be problematic as they are particularly sensitive to the toxic effects of some NSAIDs such as Paracetamol (Acetaminophen), Ibuprofen or Naproxen. The deficiency of their hepatic glutathione-dependent enzyme system, which is involved in the metabolism of NSAIDs, leads to a build-up of toxic levels of active metabolites. Accumulated metabolites can cause severe hepatocellular necrosis and methaemoglobinemia, the disorder of red blood cells (Löscher et al 1999).

Due to the described risks regarding mid- and long-term adverse effects of pain killers, there is also a strong need for alternative treatment addressing the cause of the disease.

Causal treatment

Stimulation of joint cartilage metabolism and an increased production of extracellular matrix (ECM) could slow down the progression of osteoarthritis (OA) and thus counteract wear and tear processes and break the vicious cycle of joint degeneration. Bioactive Collagen Peptides® (BCP®) are a meaningful approach with focus on the causal loop of OA. Several clinical studies with different species (mouse, dog, horse) have demonstrated the efficacy of Bioactive Collagen Peptides® (BCP®) as potential therapeutic agents and nutritional supplements for the management of OA and supporting the maintenance of joint health in animals.

In recent years of intensive research, the principle mechanism of action of Bioactive Collagen Peptides (BCP®) has been elucidated and its bioavailability and efficacy in different body tissues and cell types has been investigated.



Randomized observational study on horses

In a monocentric observational study, the efficacy of orally administered SYNOVIUM®AGILITY in two different dosages was examined on OA horses over a treatment period of 12 weeks.

18 horses without discrimination in sex, age, weight or breed were included and subdivided in group I (12 horses) and group II (6 horses). Group I was treated with 50 g and group II with 25 g daily dosage of SYNOVIUM®AGILITY supplemented into standard horse fodder.

At baseline, both treatment groups were tested for statistically significant differences in body weight, age and degree of lameness. Data revealed no statistically significant differences between the SYNOVIUM®AGILITY dosage groups. The grade of lameness was evaluated by the attending veterinarians according to Taylor & Hillyer Score (Taylor & Hillyer 1997). Moreover, a bending test of the affected ankle and the turn pain while in gait were evaluated after a 1-4 score scale (1 = negative, not existing; 2 = slightly positive, 3 = moderate; 4 = strong). Examination was done at the starting point, after 6 and 12 weeks.

The progress of OA was also assessed by the horse owners on a weekly basis. The progression of vitality, mobility and lameness were subsequently classified as better, unchanged or worse in comparison with the previous week. At the end of the study, the overall treatment success was evaluated as excellent, good, acceptable, poor or very poor.

The results of the study demonstrated that both SYNOVIUM®AGILITY dosages showed positive effects in all test parameters and no statistically significant differences between group I with high (50g/day) and group II with low (25g/day) dosage could be observed.

As shown in Fig. 20 (still confidential), the degree of lameness was already improved after 6 weeks of 50g SYNOVIUM®AGILITY ingestion. This pronounced improvement was also determined after treatment with a daily dosage of 25 g, although the level of statistically significant differences to baseline was not achieved, possibly due to the small group size of only 6 horses. In addition, the positive findings in group I with 50 g SYNOVIUM®AGILITY administration showed a statistically significant improvement in the bending test (Fig.21) as well as a reduction of turn pain (Fig.22).

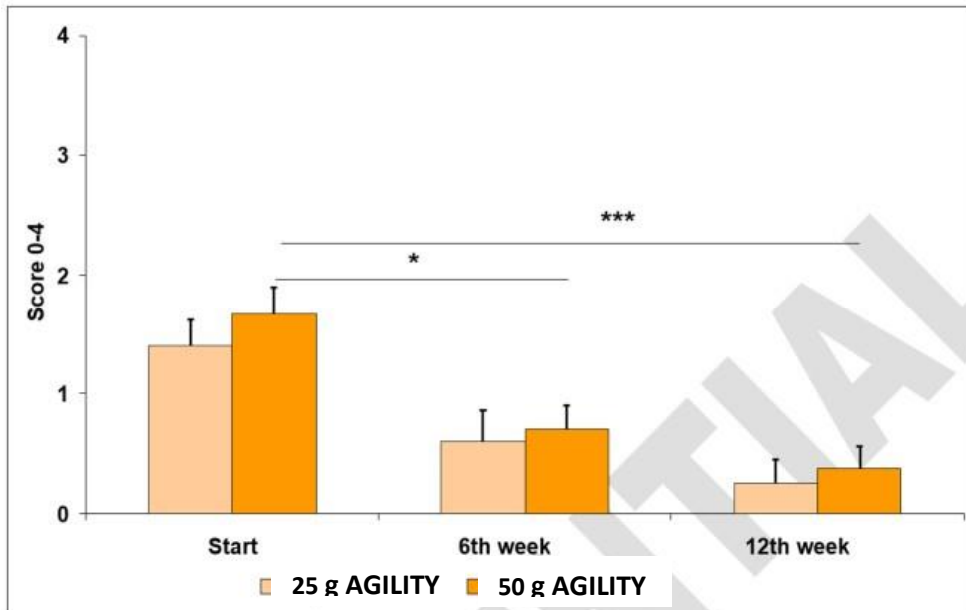


Fig.20

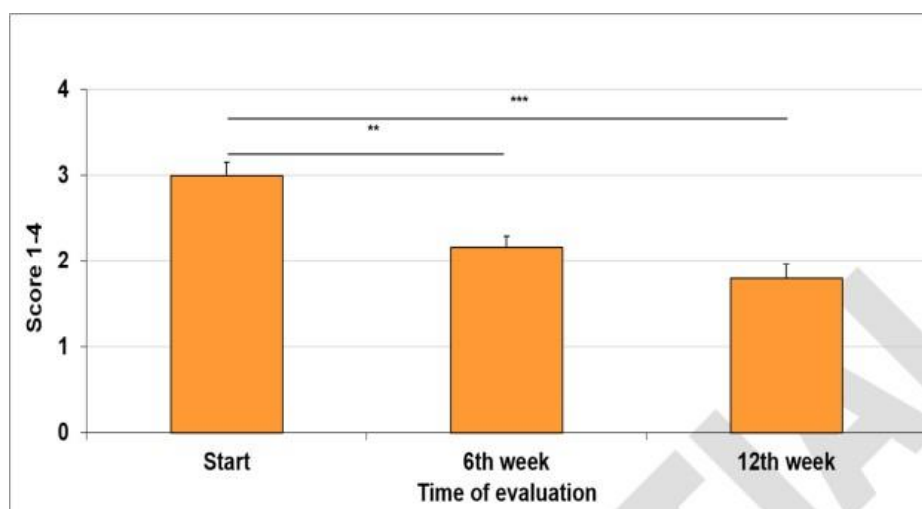


Fig.21 A statistically significant improvement of the bending test was determined by the veterinarian after 50 g AGILITY administration (n = 12, ***-** p < 0.001-0.01, mean ± SEM).

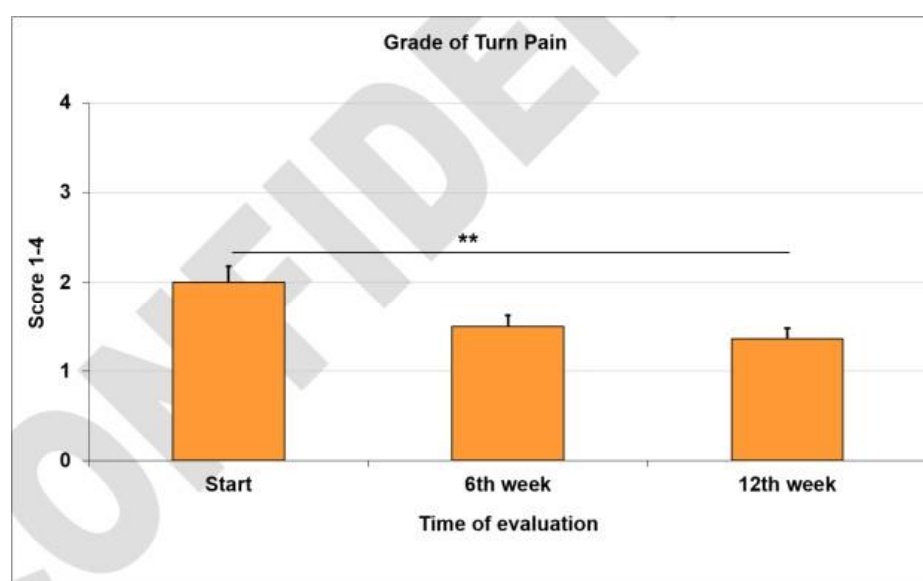


Fig.22 Turn pain on a hard floor was statistically significantly reduced, as determined by the veterinarian, after 50 g AGILITY per day.

IV Placebo-controlled study with senior horses

In a monocentric placebo-controlled study, the efficacy of orally administered SYNOVIUM®AGILITY on chronically arthritic horses was examined in comparison with a placebo over a treatment period of 12 weeks. 20 horses without discrimination in sex, age, weight or breed were available for this study and sub-divided into 10 horses per treatment group.

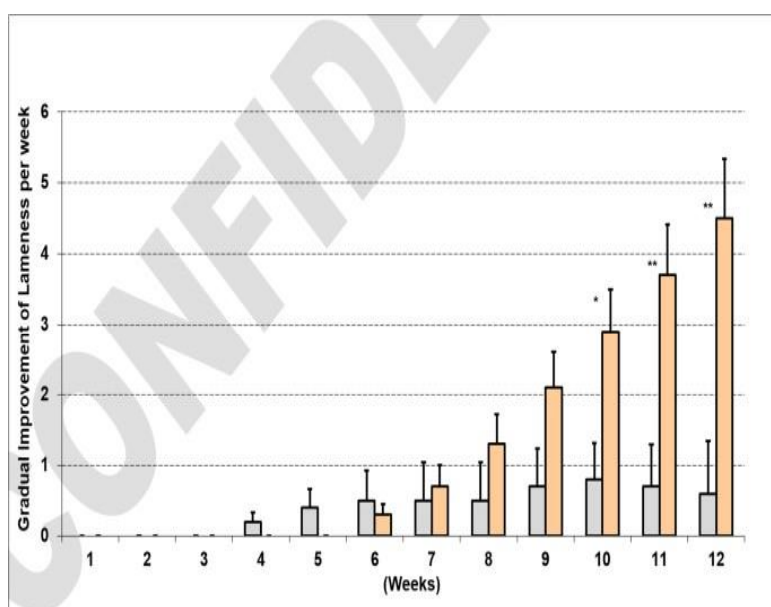
The average age of horses was 18.2 years. The groups were treated with 25 g daily dosages of SYNOVIUM®AGILITY or maltodextrin as a



placebo supplemented into the regular horse fodder. A mean degree of lameness of 1.7 ± 0.8 (Taylor & Hillyer Score, as mentioned in previous III - Randomized Observational Study with horses) was evaluated by veterinarians at baseline values.

The progress of osteoarthritis (OA) was evaluated by horse owners on a weekly basis in comparison with the previous week.

As shown in Fig. 25, the degree of lameness was statistically improved after 12 weeks of SYNOVIUM®AGILITY feeding. Interestingly, this improvement of lameness was a statistically significant increase in comparison with placebo-treated horses, where the degree of lameness was unchanged.



Conclusions from clinical horse studies

In both studies on adult and senior horses, the positive impact of SYNOVIUM®AGILITY administration on the treatment of OA was demonstrated. SYNOVIUM®AGILITY has a high degree of acceptance by horse owners and lameness was improved. The positive impact of low SYNOVIUM®AGILITY dosage was shown in comparison to the placebo treatment.

Overall conclusions

Several clinical studies in dogs and horses including a wide spectrum of heterogeneous types have demonstrated the efficacy of a SYNOVIUM®AGILITY treatment in the management of OA. The nutritional supplement SYNOVIUM®AGILITY addresses the cause of the disease by stimulating joint cartilage metabolism. Due to an increased production of extracellular matrix (ECM), SYNOVIUM®AGILITY was able to slow down the progression of osteoarthritis (OA) and break the vicious cycle of joint degeneration.



Overall, the clinical situation of the dogs was statistically significantly improved by a SYNOVIUM®AGILITY treatment of 5g per day. In dogs having received 2.5g of SYNOVIUM®AGILITY per day, the degree of lameness was improved by trend. Based on the existing data on OA dogs, there is a high likelihood that similar positive effects could be expected in cats suffering from osteoarthritis.

Additional studies on adult and senior horses demonstrated the positive impact of SYNOVIUM®AGILITY treatment. Overall, the clinical situation of horses was already improved by a SYNOVIUM®AGILITY supplementation of 25g per day compared to a placebo group. Based on the current data, it can be concluded that the oral administration of SYNOVIUM®AGILITY has a beneficial effect on OA in dogs and horses.

Consequently, supplementation of SYNOVIUM®AGILITY Bioactive Collagen Peptides can help to improve and maintain joint health and contribute towards preserving mobility and quality of life.