ARTHRAMID®

by contura vet

ARTHRAMID® | 2.5% iPAAG®

Equine Clinical White Paper

Mechanism of Action · Clinical evidence
Safety · Practical application

2.5% iPAAG®

Arthramid® Equine White Paper 2026

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Executive Summary

Osteoarthritis (OA) is cited as the most important musculoskeletal disorder in both humans and horses.

Clinically, it is associated with lameness and dysfunction of the affected joint, and approximately 60% of all equine lameness is due to OA.

> Significant economic loss to the equine industry occurs as a result and, coupled with welfare concerns, motivates ongoing research into innovative treatments.

The rapid resolution of lameness by a reduction in pain is paramount, but treatments, ideally, should also serve to arrest or slow the progression of the disease.

Conventional therapeutic approaches include non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, which provide short-term pain relief through their anti-inflammatory effects but are associated with potential adverse effects and have limited disease-modifying capacity.

In addition, a range of symptom-modifying osteoarthritis (OA) treatments are used, including hyaluronic acid (HA), polysulphated glycosaminoglycans (PSGAGs), pentosan polysulphate (PPS), platelet-rich plasma (PRP), interleukin-1 receptor antagonists (IRAP), and mesenchymal stem cells (MSCs).



Arthramid® is a non-absorbable, injectable 2.5% polyacrylamide hydrogel (iPAAG) designed for intra-articular administration. It is indicated for the treatment of lameness in horses due to non-infectious inflammation of joints, including OA. Extensive preclinical and clinical evaluations show that Arthramid is biocompatible, non-toxic and non-neurotoxic, and treatment with Arthramid demonstrates a very low rate of adverse events, even with repeated use.

Arthramid is a synovial implant and unlike conventional treatments of OA, acts through a mechanical and structural mode of action. Its primary intended purpose is to restore synovial membrane elasticity, thereby improving joint function, reducing pain and influencing disease progression.

After intra-articular injection, Arthramid integrates into the synovial membrane, where it reduces tissue stiffness and fibrosis, hence restoring elasticity. This leads to improved joint mobility and reduced joint pain. Evidence also suggests Arthramid may also modulate inflammatory pathways and gene expression linked to OA progression as secondary, downstream effects to the implantation.

Multiple clinical studies have demonstrated that treatment with Arthramid results in significant and sustained reduction in lameness and enables a substantial proportion of treated horses to return to full or improved function.

> Arthramid therefore provides superior and longer-lasting effects compared to alternative intra-articular therapies and, in direct comparative studies, outperforms corticosteroids and HA at later timepoints.

In conclusion, Arthramid represents a new therapeutic approach to treating equine OA by targeting the mechanical properties of the synovium and potentially modifying disease progression. Clinical data support its efficacy, durability of effect and strong safety profile, positioning it as a first-choice treatment option for equine OA.

Therapies for Treatment of Osteoarthritis

In companion animals, osteoarthritis (OA) is generally treated symptomatically[1].

> The challenge is to develop therapeutic options that are both pain-reducing and disease-modifying since such treatments will not only improve the activity level and quality of life for the affected animals, but also slow, delay, or reverse the progression of the deleterious effects OA has on the articular cartilage and surrounding joint structures.

Selected current therapies are briefly listed below.

1.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are readily available, cost-effective drugs for the treatment of OA. The drugs have an anti-inflammatory effect and thereby both reduce pain and slow the progression of the disease. NSAIDs can be administered both systemically and topically and are subdivided into selective and non-selective COX inhibitors. The symptom-modifying effects are reported to be short-term and the drugs can cause adverse changes in healthy joint tissue[2].

Treatment with Arthramid can be combined with administration of NSAIDs for immediate pain relief.

1.2 Corticosteroids

Corticosteroids have analgesic effects in OA due to their anti-inflammatory action, and intra-articular corticosteroid administration is one of the most common treatments of OA[3]. In general, intra-articular



treatment with corticosteroids alone or in combination with e.g. Hyaluronic Acid (HA) produces positive but short-term effects, although detrimental effects are also reported[3-5]. The conflicting data may be related to time- and dose-dependent effects leading to a switch from positive to negative effects with increasing concentrations or treatment durations[4]. Concerns for its ongoing use include steroid-induced deterioration of articular tissues, known as “steroid arthropathy”. Thus, the overuse of a treated joint can also result in accelerated cartilage degeneration[6]. These primary concerns are compounded by additional reports of the adverse effects of corticosteroids on chondrocyte metabolism[7].

A comparison between the corticosteroid triamcinolone acetonide (TA) and Arthramid for the treatment of lameness related to the middle carpal joint in thoroughbred racing horses concluded that Arthramid was statistically significantly superior in reducing lameness at 6 weeks after treatment[8].

1.3 Symptom-modifying OA drugs

Several drugs have been investigated as potential Symptom-Modifying OA Drugs (SMOADs), defined as drugs that can delay, stabilise or repair OA lesions in the affected joints.

HYALURONIC ACID (HA)

Hyaluronic Acid (HA) is a naturally occurring proteoglycan that has been used for the treatment of equine OA for several decades and has been the topic of multiple studies[9]. In addition to facilitating joint lubrication and contributing to the viscoelasticity of the synovial fluid, HA is also proposed to be a free radical scavenger and to have anti-inflammatory, immunomodulatory, analgesic and chondroprotective properties[9,10].

Despite the many reported beneficial effects of HA some studies also reveal that HA has a short metabolic half-life. In one study of intra-articular administration of HA, the concentration of HA was not significantly different from control values within 24 hours of administration[10] and, although the clinical effects of HA products are reported to be longer than the half-life of the injected HA,[9] the overall data on the clinical effects of intra-articular HA treatment are variable and inconsistent[11].

A clinical trial comparison between HA (Hyonate®) and Arthramid for the treatment of lameness related to the middle carpal joint in thoroughbred racing horses concluded that Arthramid was statistically significantly superior in reducing lameness at 6 weeks after treatment[8].

POLYSULPHATED GLYCOSAMINOGLYCANS (PSGAG)

Polysulphated Glycosaminoglycans (PSGAGs) are low-molecular-weight polysulphated glycosaminoglycans (GAGs). They are a naturally occurring element that in the presented form resembles chondroitin sulphate from healthy cartilage. The product is suggested to inhibit matrix metalloproteinases and is marketed (Adequan®) for equine use. The product is primarily suggested to prevent OA by slowing down morphological changes in cartilaginous lesions[12,13].

PENTOSAN POLYSULPHATE (PPS)

Pentosan polysulphate (PPS) is a small, semi-synthetic, heparan sulphate-like molecule that has tissue-protective properties e.g. by working as a protease and NGF inhibitor, and by regulating complement activation and promoting the production of hyaluronan[14]. PPS is marketed (Zycosan™) for equine use[13].

PLATELET-RICH PLASMA (PRP)

Platelet-rich plasma (PRP) is a blood-derived product that consists of plasma with a higher concentration of platelets than is present in peripheral blood. Platelets release growth factors that can stimulate processes like chondrocyte proliferation and reduce signalling that promotes chondrocyte apoptosis[12].

PRP is obtained by drawing blood samples from the affected animal. After processing, the enriched blood is administered by intra-articular injection into the affected joint[12].

Clinical data on the use of PRP for the treatment of OA are still limited, but overall they indicate a promising clinical effect[11]. In one survey of equine practitioners, the procedure was used almost exclusively to treat tendon or ligament injuries[15].

INTERLEUKIN-1 RECEPTOR ANTAGONIST PROTEIN/AUTOLOGOUS CONDITIONED SERUM (IRAP/ACS).

Interleukin 1β (IL-1β) is a pro-inflammatory cytokine with multiple functions in the development and progression of OA. The signalling induced by IL-1β can be competitively inhibited by the protein Interleukin-1 receptor antagonist (IL-1Ra) that binds the same receptor as IL-1β but without activating the receptor[16].

Like PRP treatment, IL1Ra treatment is performed by reinjecting the patient's own blood following a processing step. The procedure has produced promising results with long-term effects[16].

MESENCHYMAL STEM CELLS (MSC)

Mesenchymal stem cells (MSCs) are pluripotent cells that possess the potential of stimulating cartilage formation and vascularization and have anti-inflammatory and immunoregulatory potentials. The cells are obtained e.g. from the patient's own tissue and are re-introduced into the OA-affected joint following a processing step[17,18].

Clinical studies with intra-articular injections with MSCs in horses for the treatment of OA produced promising clinical effects. However, the treatment is expensive and produces variable results[11]. Moreover, there is a lack of consensus in cell sources, dosage and administration procedures, and it has been suggested that focus should be on establishing cell-free procedures using molecules derived from MSCs[19,20].

1.4 Arthramid

PRODUCT DESCRIPTION

Arthramid is a biocompatible, non-absorbable, non-pyrogenic, injectable, transparent polyacrylamide hydrogel for intra-articular injection in animals.

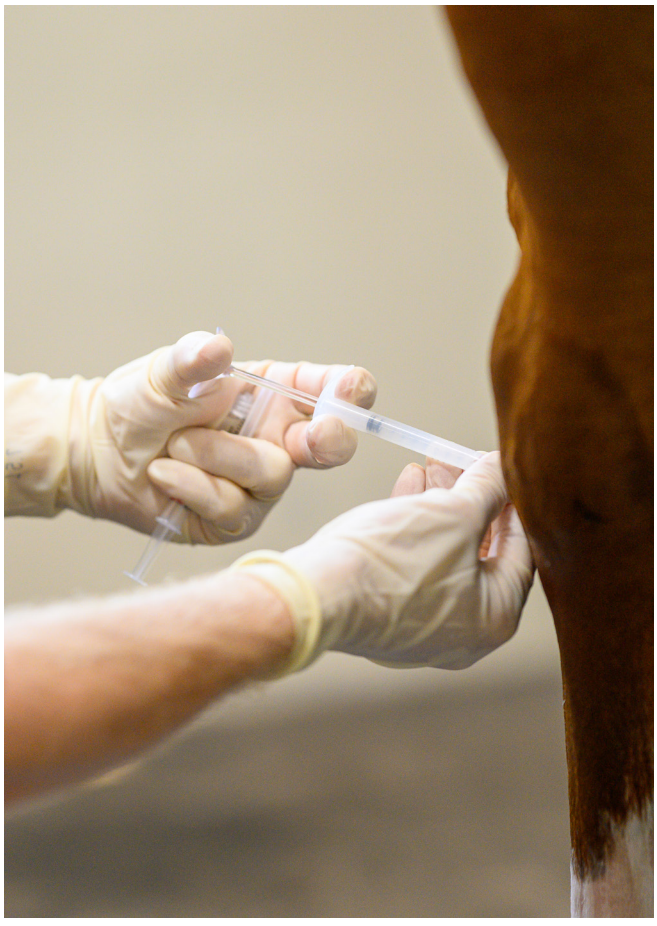
Arthramid consists of approximately 2.5% cross-linked polyacrylamide and 97.5% water for injection. The hydrogel is supplied in a sterile pre-filled 1 mL syringe sealed with a Luer lock fitting.

INDICATION FOR USE

Arthramid is indicated for the treatment of lameness in horses due to non-infectious inflammation of joints.

PRIMARY INTENDED PURPOSE

The Arthramid hydrogel is designed and intended specifically to restore synovial elasticity in patients with OA, ameliorating joint mobility and range of motion.



Osteoarthritis (OA) is a common chronic joint illness in both humans and companion animals.

It is a slowly progressive disease leading to joint pain, joint stiffness and swelling, and decreased range of motion of joints [11,21,22].

In the horse, the joints affected by OA depends highly on the type of activities the animals are performing[23]. However, OA is a common disease in all types of horses and up to 60% of all cases of lameness observed in horses have been estimated to be related to OA[24].

Current treatments for OA usually focus on management of pain and inflammation but rarely affect the progression of the disease[23].

Arthramid is a hydrogel product for intra-articular injection intended for the management of non-infectious causes of joint disease in horses.

After injection, the hydrogel becomes incorporated into the synovial membrane where its presence restores the elasticity of the synovial tissue, hence reducing stiffness and fibrosis, improving joint mobility and reducing joint pain.

Thus, rather than simply relieving the symptoms of OA, Arthramid offers a minimally invasive way to impact the progression of the disease.



2.1 Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease characterized by synovial inflammation and the progressive alteration and degradation of the subchondral bone and articular cartilage. The disease leads to pain, swelling and stiffness of the affected joint, and reduced joint mobility[22].

In horses, the combined effects of joint pain, stiffness and swelling will lead to alterations in the gait, which will be perceived as lameness.

In addition to the physical impact of the disease, OA can also have behavioural and social effects[25], and in particular for horses, the disease affects not only the quality of life but can also have significant financial consequences and lead to periods of inactivity[26-28].

EPIDEMIOLOGY

In the veterinary field, OA is recognized as a major health issue in horses[29], as well as e.g. dogs, cats and cattle[30-32], and humans, horses, dogs and cats share many joint-related degenerative conditions leading to OA[33].

Equine OA is a common disease causing both pain and lameness[23,34]. The prevalence of OA in horses older than 15 years is greater than 50% increasing to 80-90% for horses older than 30 years[35].

The occurrence of OA is observed in leisure horses as well as e.g. thoroughbred racehorses[36], show jump horses[23,37] and western performance horses[38], but due to the different types of activities the typically affected joints may not be the same[23].

AETIOLOGY

The pathogenesis of OA is multifactorial and is in humans known to include genetic factors[39,40]. However, equine OA, is most often related to post-traumatic responses induced by the high-performance activity of the animals[11,23], with or without underlying conformational faults that alter mechanical stresses through the joint, or developmental orthopaedic diseases where the cartilage is principally defective and will fail under normal load[41].

That said, innate immune signalling pathways play an important role in potentiating the OA disease and in an equine model of post-traumatic OA, differentially regulated genes were identified in 17 signalling pathways related to extra-cellular matrix (ECM) turnover, protein metabolism and growth factor signalling[42].

Moreover, following restoration of synovial elasticity after Arthramid treatment in equine osteoarthritic joints, synovial transcriptomic analyses have

demonstrated upregulation of innate immune and cell cycle regulatory pathways, alongside suppression of certain inflammatory pathways[43]. Further studies are justified to expand upon these findings.

PATHOPHYSIOLOGY

The two primary functions of a synovial joint are to enable efficient movement and to transfer load[41,44]. These functions are facilitated by several tissues that all can be affected by injury, including the subchondral bone, articular cartilage, synovium and joint capsule, as well as the intra-articular and extra-articular ligaments and, if present, the meniscus[45-48]. All these tissues interact with each other, either directly or via the synovial fluid[49].

OA is not a single disease, but a syndrome or a group of disorders characterized by a common end stage: the progressive deterioration of the articular cartilage accompanied by changes in the bone and soft tissues of the joint[24,50].

There are multiple studies indicating that synovitis is an essential component in its pathogenesis[6,41,51,52], and it is well recognized that the OA disease process starts with alterations in the synovial membrane, fibrous joint capsule, subchondral bone, or ligaments, as well as the articular cartilage or any combination of the above[53].

In athletic and young horses, synovitis and capsulitis are changes that occur early on and they are assumed to be associated with repetitive trauma[41,54]. This etiology originates most often from overuse and conformational problems predisposing the horse to inappropriate biomechanical forces on the articular cartilage[41].

Inflammatory mediators (cytokines, prostaglandin E2 and matrix metalloproteinases) are released by reactive synovial cells in response to cartilage wear, and occur in both naturally and experimentally induced OA[55-59].

Clinically, synovitis is seen as a palpable joint swelling due to either synovial effusion or thickening of the synovium[60,61].

If this condition persists, fibrosis and increased friction in the joint capsule will develop, resulting in thickening of the joint capsule and loss of the normal range of joint motion[62]. Moreover, synovitis induces cartilage matrix degradation[54]. Therefore, rapid resolution of synovitis and capsulitis is critical in the management of OA.

OSTEOARTHRITIS AT THE HISTOLOGICAL LEVEL

The synovial intima is lined by a diverse population of synoviocytes, classified according to their ultrastructure as type A, B, C cells[55].

Type A cells are macrophages, implicated in phagocytosis of fluid, foreign material and microbes; type B cells are fibroblasts; locally derived cells that

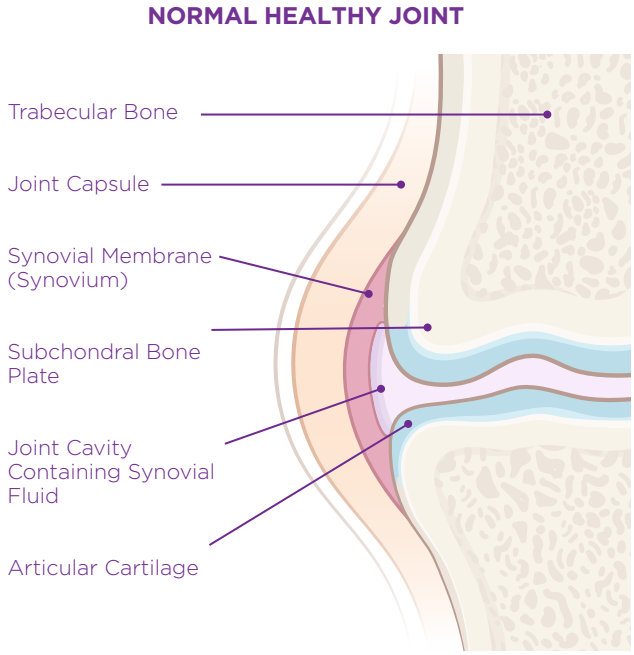


Figure 1. Normal joint anatomy.

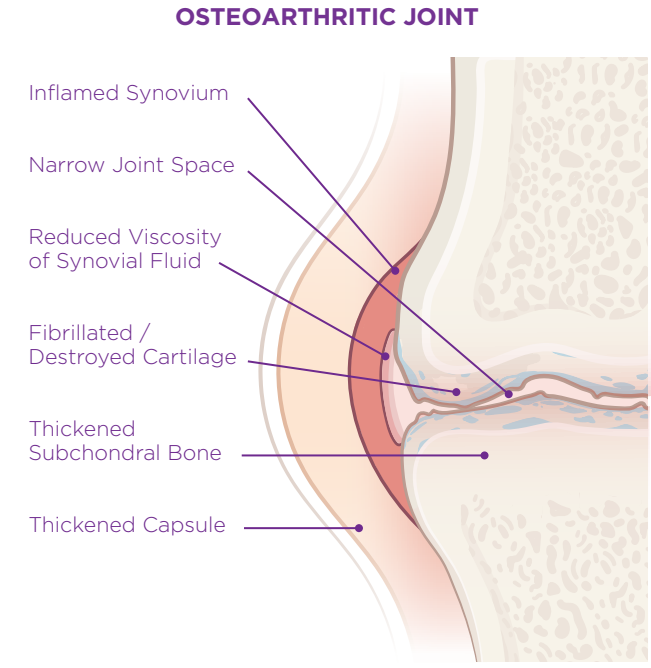


Figure 2. Pathological changes associated with osteoarthritis.

produce structural components including collagen[63]; and type C cells appear to be an intermediate between the type A and B forms. Beneath this cellular layer of synoviocytes is the subintima, comprised of fibrous and adipose tissue, with blood vessels and small numbers of immune cells.

The deepest layer is comprised of loose connective tissue that allows the membrane to move freely. Ligaments, tendons or capsular fibrous tissue are located outside of that layer[55].

Multiple pathologic states induced by single or repetitive traumas form the initial "take-off" for the disease progression towards OA. These states can include traumatic injury, synovitis, capsulitis, sprain, intra-articular fractures and meniscal tears[41,54], all of which lead to a common final end-stage of joint failure[41,64-67].

STRUCTURAL DAMAGE

Synovial lining cells produce e.g. the proteins lubricin and hyaluronic acid (HA), which together reduce joint friction by providing boundary lubrication at the articular surfaces. One observed aspect in relation to OA is alterations in the rheological behaviour of the synovial fluid including changes in the viscoelastic properties,[68] and may contribute to the deterioration of articular cartilage in joint disease and after joint injury[34]. Furthermore, the synovial membrane becomes a source of proinflammatory and catabolic products, which contribute to articular matrix degradation[66,69].

Although structural joint damage in OA is a constant feature, the clinical syndrome of OA is quite variable, with differences in affected joint patterns, risk factors, rates of progression and severity of symptoms[70]. It is recognized that early structural changes seen associated with OA may remain asymptomatic for many years[49].

INFLAMMATION AND SYNOVITIS

Inflammation is most pronounced in acute synovitis and is one of the initial changes to occur in the development of OA[24,47,60]. Furthermore, the presence of synovitis in OA is associated with more severe pain, joint swelling and joint dysfunction[60,71].

PAIN AND SYNOVITIS

In synovial joints two general types of pain stimuli can be distinguished: mechanical stimuli, generated by mechanical changes in the environment of the joint (e.g., by direct trauma), and chemical stimuli resulting from tissue inflammation[6]. The stimuli are detected and forwarded by different types of receptors, mechanoreceptors and nociceptors, to peripheral nerves, and via the spinal cord ultimately to the brain to be processed, modulated and perceived.

The rapid resolution of lameness attributable to pain is noticeably the principal concern of owners and trainers and the reason why horses are presented for veterinary care[7,72]. The single most important factor that contributes to the pain of OA is synovitis that, through joint effusion, swelling and capsulitis, in turn will activate mechanoreceptors in the joint capsule and result in direct chemical stimulation of nociceptors[6]. In contrast, there is only a weak correlation between the observed severity of articular damage and the magnitude of pain[55].

Articular tissues contain four types of afferent receptors; the mechanosensitive Piezo ion channels are of particular interest. These proteins are located in chondrocytes and synovial cells and are reported to contribute to pathophysiological remodelling of cartilage and the inflammatory responses observed in relation to OA by responding to variations in mechanical loading[73,74].

In addition to mechanoreceptors stimulated by mechanical influences, some receptors can become hypersensitized by chemical stimuli released during the inflammatory process[6].

Joint pain related to OA is therefore attributable to synovitis and capsulitis as well as subchondral bone exposure, remodelling or bone marrow oedema, and marginal periosteal activation associated with osteophytosis[75].

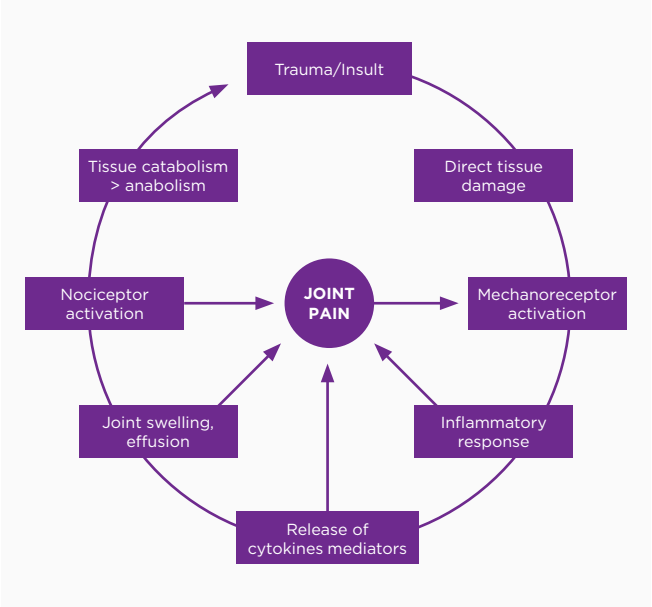


Figure 3. Simplified schematic diagram of the vicious cycle of osteochondral damage and cartilage degeneration in OA, showing key processes that may contribute to joint pain associated with disease.

Adapted from van Weeren P.R, de Grauw J.C 2010[6]

3.1 Chemistry & Manufacturing

Arthramid and other Contura products like Arthrosamid®, Bulkamid® and Mictamid® all contain the same injectable hydrogel 2.5% cross-linked polyacrylamide and 97.5% water for injection. Consequently, this hydrogel is commonly referred to as "injectable 2.5% polyacrylamide hydrogel" or simply 2.5% iPAAG.

CHEMISTRY

Polyacrylamide is a polymer made from monomeric acrylamide (AM; CAS no. 79-06-1). The polymerization of AM to polyacrylamide is induced by generating free radicals of AM that can react with other AM molecules to form linear strands of polyacrylamide where the individual AM molecules are combined by covalent single carbon-carbon bonds.

To obtain a cross-linked polyacrylamide hydrogel the polymerization of AM is performed in the presence of N,N-methylene-bis acrylamide (MBAM; CAS no. 110-26-99).

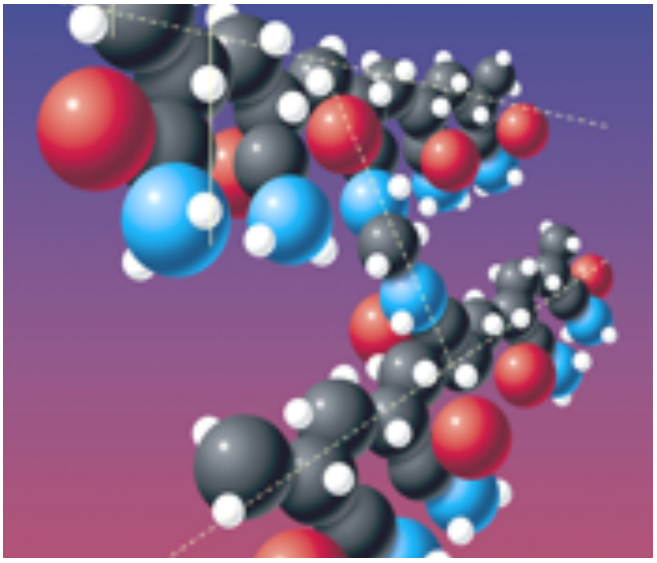


Figure 4. 3D molecular representation of 2.5% iPAAG showing cross-linking between two molecules of polyacrylamide.

MANUFACTURING

The Arthramid is manufactured by Contura International A/S in Denmark at an ISO 13485 and GMP-certified facility.

The 2.5% iPAAG is generated by a patented procedure called In-line Cross-Linking Technology (ILX Technology) performed with equipment located in a clean room environment. To minimize operator interaction as far as possible the procedure is performed using closed compartment processes and a very high degree of automation.

The manufacture of the 2.5% iPAAG includes multiple washing steps to minimize the presence of residual monomers. Consequently, the concentrations of residual AM and MBAM in the final hydrogel are below 1.5 ppm and 1.0 ppm, respectively.

As a final step of the manufacture of the 2.5% iPAAG the hydrogel is homogenized to be transformed into an injectable form.





The highly reproducible manufacturing procedure result is a homogeneous 3-dimensional polymer composed of 2.5% cross-linked polyacrylamide with approximately 500 repeating units of acrylamide per cross-linking bis-acrylamide unit and 7-14 cross-links per chain fragment in the homogenized gel. The hydrogel contains 97.5% water, where the individual water molecules interact with the polyacrylamide chains primarily through hydrogen bonds to amide groups of the polymer.

3.2 Differences Between Polyacrylamide Hydrogels

Depending on the manufacturing process polyacrylamide hydrogels can be produced to contain different concentrations of polyacrylamide, different degrees of cross-linking, different average molecular weights etc.

These differences in polyacrylamide specifications have profound implications on their characteristics,[76] and consequently on their behaviour in tissues and subsequent mode of action.

All polyacrylamide hydrogels are known to have high lubricating properties that potentially are better than those of HA[77].

Accordingly, the mode of action of one polyacrylamide hydrogel product is reported to be to lubricate damaged cartilage surfaces while being slowly phagocytosed by macrophages[78].

> The Contura 2.5% iPAAG has a chemical structure and molecular weight that makes the hydrogel highly stable[76,79].

There is a well-described relationship between particle size and the risk for tissue migration, and in soft tissue injection sites there is an interrelationship between particle size, phagocytosis, tissue mobility and tissue immobilization[80].

Objects above 12-17 µm cannot be phagocytosed but are encapsulated over time and remain immobilized within soft tissues indefinitely[81,82].

In contrast, objects with a diameter below 17-20 µm can be phagocytosed and may migrate from the implant site to local draining lymph nodes to be distributed systemically[80,83].

The average size of an individual 2.5% iPAAG molecule is much larger than 17-20 µm (only ~10% of the molecules are smaller than 332 µm) and the size-distribution-curve indicates that particles with a diameter below the 17-20 µm threshold are essentially not present in the product.

Consequently, the Contura 2.5% iPAAG has characteristics that ensure that the gel is not phagocytosed and that the individual hydrogel molecules do not migrate from the implant site.

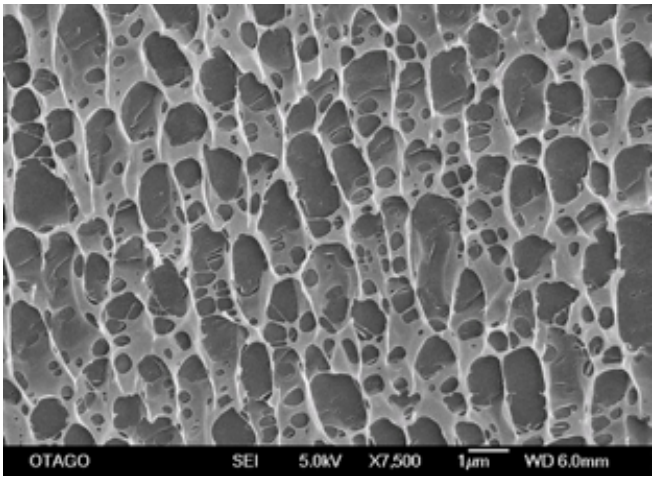
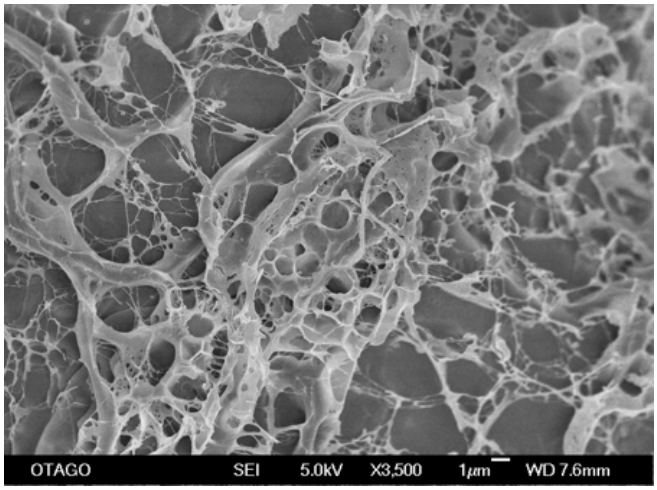
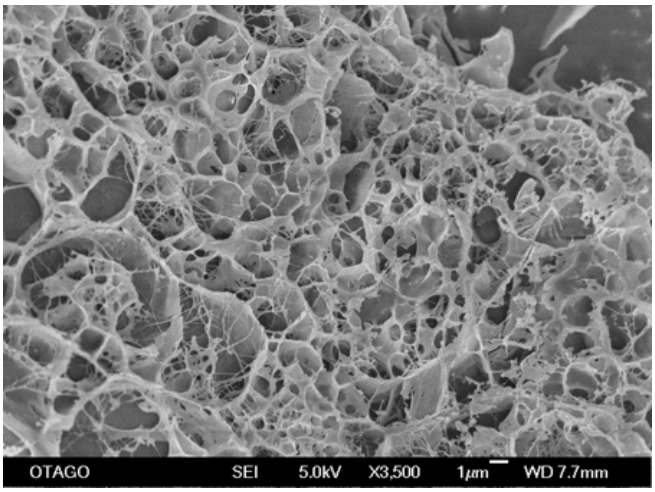


Figure 5. Scanning electron micrograph of neat 2.5% iPAAG hydrogel. Scale bar = 1.0 µm, demonstrating the material's porous and homogeneous structure.



Figures 6 and 7; Scanning electron microscopy images from treated joints at 28 and 42 days post-injection of 2.5% iPAAG. Within the synovial subintima,[85] the gel demonstrates integration with the surrounding tissue via fine collagen fibres, resulting in the formation of a stable three-dimensional hydrogel scaffold. Scale bar = 1.0 µm.



The Arthramid 2.5% iPAAG is injected directly into the intra-articular space of OA joints.

Immediately after injection, the 2.5% iPAAG is located in the intra-articular space where it increases the viscosity of the synovial fluid,[84] but within ~14 days[85] the 2.5% iPAAG relocates to the synovial membrane[85] where it remains to become stably integrated into the synovial tissue[86].

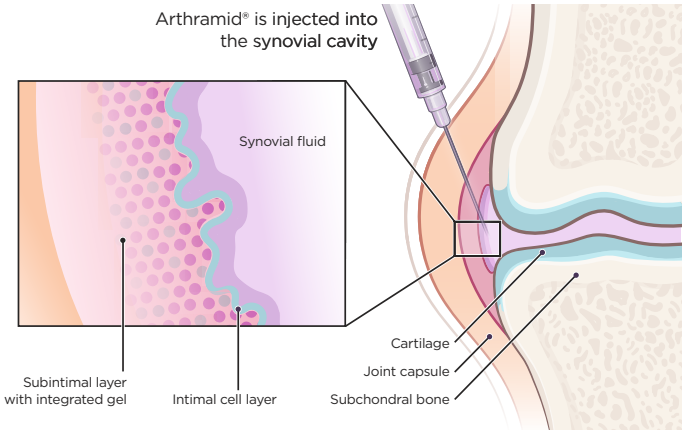


Figure 8. Schematic demonstrating relocation of gel into the subintima of the synovium.

Following injection, the 2.5% iPAAG, like any other foreign substance injected into the body, gives rise to a low-level foreign body response, which includes an initial increase in the number of synovial host cells with macrophage characteristics. These cells infiltrate the 2.5% iPAAG, but with no evidence of neutrophilic inflammation, fibrin deposition, cell death or other inflammatory cell types[85].

Over time the 2.5% iPAAG gradually becomes integrated with the surrounding tissue via thin strands of collagen fibres, and the infiltrating cells gradually transform into fibroblasts and endothelial cells, which eventually form a thin vessel-bearing fibrous network inside the 2.5% iPAAG with no evidence of fibrosis or mineralization[84,85].

At 3 months post-injection, synovial cells restore the lining of the synovial membrane.

The result is a vascularized network of connective tissue fibres embedded within and around the injected 2.5% iPAAG,[84,87] and a restored inner synovial lining (2-4 layers of synovial cells), which prevents access of the 2.5% iPAAG to the joint cavity.

In the horse the thickness of the synovial lining layer is demonstrated to increase 5-10 fold in response to the presence of the 2.5% iPAAG for a period of at least 3-24 months post-injection[84,85].

4.1 Mode of Action

The Arthramid 2.5% iPAAG has a very low elastic modulus (35-120 Pa), several orders of magnitude lower than even the healthy synovium (180 MPa)[88]. The 2.5% iPAAG is therefore very soft and elastic compared to the surrounding synovial tissue.

Consequently, when the 2.5% iPAAG becomes incorporated into the synovial tissue, its presence within the diseased and fibrotically stiffened synovial subintima reduces the overall elastic modulus of the tissue substantially.

> Hence, following treatment with Arthramid, the physical presence of the 2.5% iPAAG in the synovial subintima increases elasticity and reduces the stiffness of the tissue, thus improving joint function (mobility and range of motion) and reducing pain.

These effects of the 2.5% iPAAG in the surrounding tissue have been demonstrated by theoretical rheological modelling[89], by ex vivo rheological measurements in goat[90] and horse joints[91], and by sonoelastographic measurements in humans in vivo (Prof. G. Hopper et al., unpublished data).

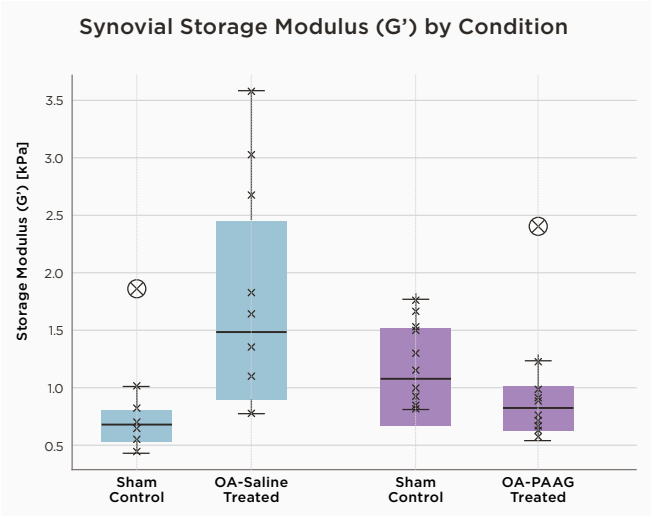


Figure 9. Joint capsule stiffness, measured as storage modulus (G'), was significantly increased in the OA limbs of the control group compared to their contralateral sham-operated limbs (1824±1105 Pa vs 1002±495 Pa; p=0.043). In contrast, OA limbs in the 2.5% iPAAG-treated group had storage moduli that were not significantly different to their contralateral sham limbs (1099±647 Pa vs 1184±504 Pa; p=0.718). Relative to the contralateral sham limb for each horse, joint capsule stiffness increased approximately 2.7-fold in saline-treated OA limbs but showed no detectable change (1.0-fold) in 2.5% iPAAG-treated OA limbs[91].

More recently, a clearer understanding has emerged regarding how restoring joint capsule elastance can interrupt the cycle of inflammation that drives the

progression of OA.

In the synovial fluid and membrane of Arthramid-treated joints, substantial changes in inflammatory gene expression have been observed—most notably, a downregulation of TNF-α and several T-cell/lymphocyte-associated pathways[43].

Newly identified mechanosensitive receptors, including Piezo channels, offer a plausible mechanistic link between treatment-induced increases in synovial elasticity and the biomolecular, transcriptomic and epigenetic remodelling detected in synovial tissue subsequent to treatment with Arthramid.

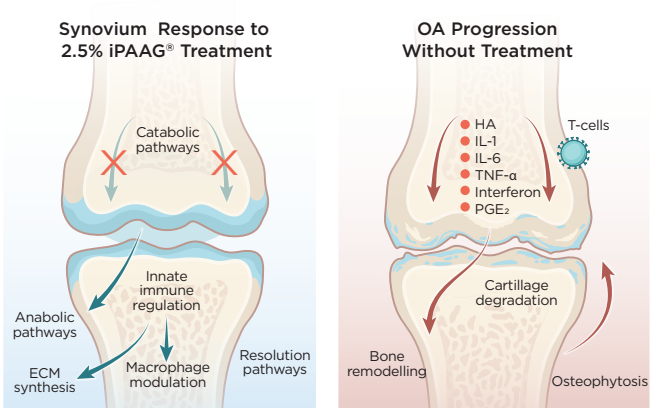


Figure 10. Schematic representation of how restoring joint capsule elastance can interrupt the cycle of inflammation that drives the progression of OA. Restoring synovial elasticity is associated with downregulation of inflammatory and catabolic pathways, and enhancement of pro-resolving, anabolic and extracellular matrix restorative responses within the joint.

This hypothesis is supported by evidence that Piezo-mediated mechano-transduction converts mechanical cues into intracellular signalling cascades that regulate pain and gene expression[92].

Additionally, multiple studies have demonstrated that mechanical forces can drive epigenetic modifications in connective-tissue cell populations[93,94].

The clinical effects of this disease modification have been characterised in recent in vivo studies demonstrating significant beneficial effects on cartilage histology scores, proteoglycan staining of articular cartilage, radiographic and clinical lameness scores[95].

56 DAYS POST-TREATMENT

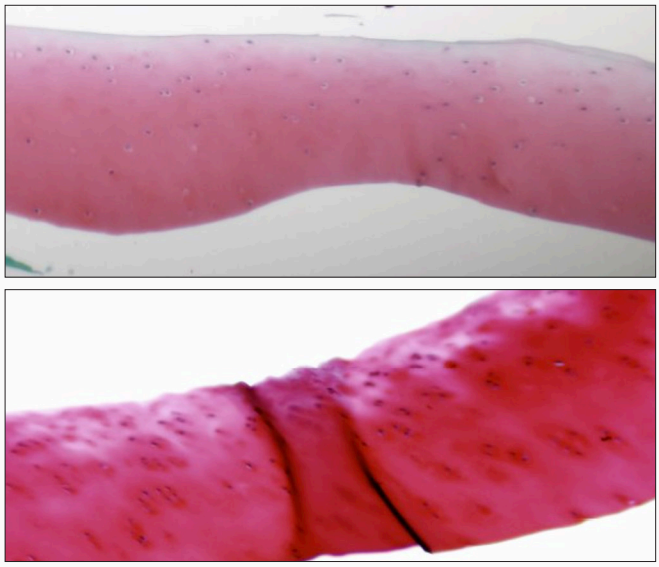


Figure 11. Representative histological sections of Safranin O and Fast Green stained articular cartilage samples from saline-treated control (top) and 2.5% iPAAG-treated (bottom) joints 56 days post-treatment. The saline control exhibits extensive depletion of matrix counterstain, indicating loss of proteoglycan content, accompanied by reduced chondrocyte cellularity. In contrast, 2.5% iPAAG-treated cartilage demonstrates preservation of proteoglycan staining and chondrocyte distribution, with maintenance of a near-normal cartilage appearance. Courtesy of Contino et al, 2025[95]. These findings suggest protection of cartilage matrix integrity following treatment with 2.5% iPAAG.

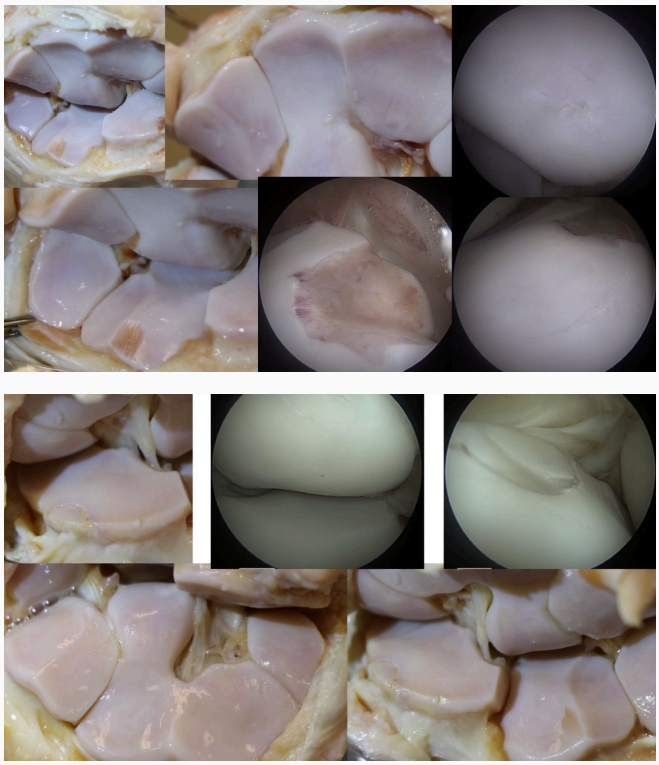


Figure 12. Representative gross and arthroscopic images of the radial facet of the third carpal bone (3CB) from saline-treated control joints (top) and 2.5% iPAAG-treated joints (bottom) following experimentally induced osteochondral fragmentation. Control joints demonstrate more extensive articular surface irregularity, fibrillation, and focal cartilage erosion within the region opposing the osteochondral fragment. In contrast, 2.5% iPAAG-treated joints exhibit a smoother articular surface with reduced evidence of cartilage damage and better preservation of overall cartilage integrity. These findings are consistent with attenuation of osteoarthritis-associated articular cartilage degeneration following treatment with 2.5% iPAAG. Images courtesy of Contino et al, 2025[95].

In one study, 12 horses diagnosed with OA to the distal interphalangeal joint, where conventional intra-articular medication had failed, were each treated with 1 mL Arthramid.

When evaluated according to the AAEP score, 7/12 horses (58%) demonstrated improvement after 1 month. After 6 months 10/12 horses (83%) demonstrated improvements, and of these 8/12 (67%) were lame-free. The remaining 2 horses (17%) were unaffected by the treatment[96].

In another study, lameness was localized to the single proximal/distal interphalangeal joints of 20 horses that had not responded to previous intra-articular treatment with corticosteroids (average duration with lameness, 15 months; average lameness score 3/10). Each horse received a single injection of 1 mL Arthramid. For 1 horse the treatment was repeated. Follow-up was performed on 18 horses with a median follow-up time of 12 months. Of these 18 horses, 12 had (67%) returned to full function, 3 (17%) to lower-level function and 3 (17%) failed to improve[97].

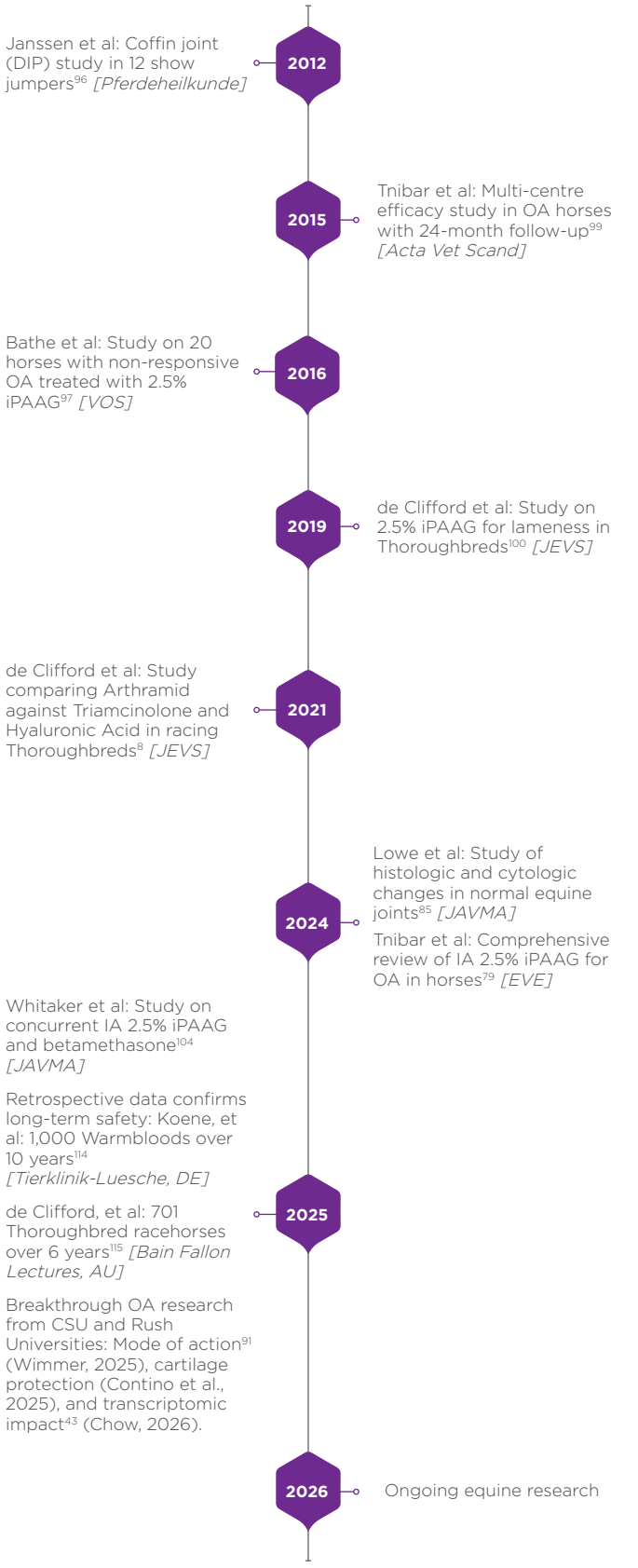
In a small study, lameness was localized to the distal interphalangeal joint of 5 horses that had previously received treatment with corticosteroids. The horses were each treated with 1 mL Arthramid. After 8 weeks 3 horses (60%) showed a significant improvement. The remaining 2 horses (40%) did not improve[98].

In a study involving 43 horses with confirmed OA in a single joint, each horse received a single 2 mL injection of Arthramid in the metacarpo (tarso)-phalangeal or carpal joint with follow-up investigations 1, 3, 6, 12, and 24 months post-injection. There was a significant decrease in lameness grade already after 1 month, and the degree of lameness and the degree of joint effusion decreased continuously throughout the period of the study[99].

In a study of 49 horses with lameness localized to the carpal or metacarpo-phalangeal joints, all horses received a single injection of 2 mL Arthramid. The initial average AAEP lameness score was 2.4. After 4, 12, and 24 weeks, the numbers of lameness-free horses were 21 (43%), 33 (67%), and 32 (65%), respectively, and already 4 weeks after treatment there was a significant reduction in the average degree of lameness ($p < 0.01$)[100].

In another seven-year multicentre study involving 312 horses, Arthramid was administered to 802 joints across three equine centres. The tarsometatarsal, fetlock, distal intertarsal and distal interphalangeal joints accounted for 90% of the treated joints. On average, 87% of the horses were reported to have a satisfactory improvement in lameness at 2 months post-injection[101].

EQUINE CLINICAL JOURNAL PUBLICATION TIMELINE



5.1 Comparisons between treatments with Arthramid, HA and TA

The effects of Arthramid on the management of lameness have been compared to both HA and TA. Horses with lameness localized to the middle carpal joint were treated with either 2 mL Arthramid, 12 mg TA, or 20 mg IA + 2 x 40 mg IV HA (administered with weekly intervals). Follow-up examinations were performed after 2, 4 and 6 weeks (and for Arthramid also after 12 weeks). There was at no time-point a significant difference between the effects of TA and HA, but after 6 weeks, the fraction of lame-free animals was significantly higher for animals treated with Arthramid (10/12; 83%) than for animals treated with HA (4/10; 40%) or TA (3/11; 27%). Animals treated with Arthramid that were lame-free after 6 weeks remained lame-free after 12 weeks[8].

In another study, 40 horses with lameness localized to the fetlock joint were treated with either Arthramid or a combination of TA and HA. At 1, 3, and 6 months post-injection the fractions of lame-free horses in the Arthramid group were 11/20 (55%), 13/20 (65%), and 15/20 (75%), respectively, whereas the fractions of lame-free horses in the TA-HA group were 3/20 (15%), 8/20 (40%), and 7/20 (35%), respectively. The reduction in lameness in response to treatment with Arthramid was statistically significantly larger than for the horses treated with HA-TA ($p < 0.001$)[102].

Recently, a systematic review of the effectiveness of treatment with 2.5% iPAAG concluded it is highly effective, lasting and safe for the treatment of equine OA[103].

MULTIPLE TREATMENTS WITH ARTHRAMID AND TREATMENT WITH ARTHRAMID IN COMBINATION WITH OTHER TREATMENTS

In a recent study, 10 healthy riding horses each received a single concurrent intra-articular injection of 1 mL 2.5% iPAAG and 1 mL (6 mg/mL) of the corticosteroid betamethasone acetate ester (BME) in a metacarpophalangeal joint.

Post-treatment examinations and evaluations were performed up to 30 days post-injection. No adverse events occurred, and it was concluded that concurrent intra-articular administration of 2.5% iPAAG and BME is safe and well-tolerated with no evidence of local or systemic adverse effects[104].

3 y.o. TB filly; 14 days; LFC Prox

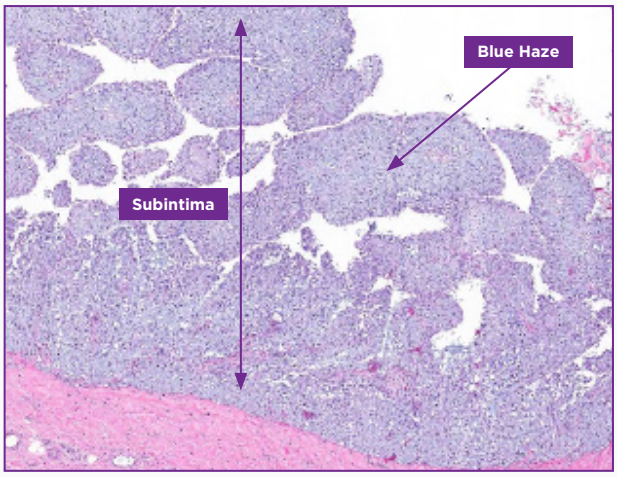


Figure 13. 14 Days post-injection: Blue haze is the 2.5% iPAAG. Cellular changes are consistent with a controlled macrophage-mediated integration response, with no histologic evidence of adverse inflammation, fibrosis, infection, or tissue injury[85].

5 y.o. TB gelding; 42 days; LFC Prox

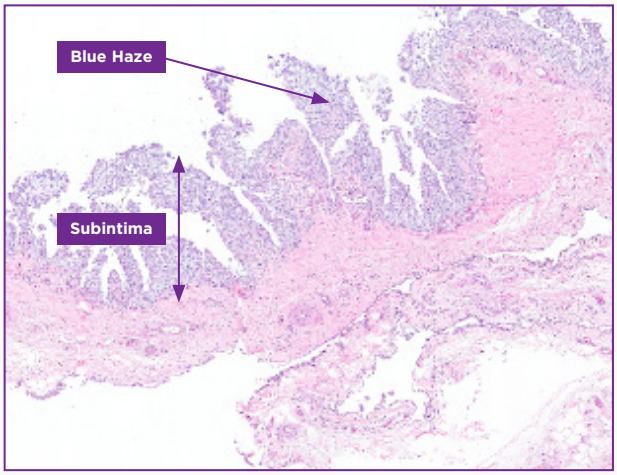


Figure 14. 42 Days post-injection. The hydrogel forms an integrated, biostable scaffold within the synovial membrane subintima layer that supports tissue adaptation while maintaining a normal tissue architecture. This is proposed to improve the viscoelastic behaviour of the synovial membrane and joint capsule, contributing to improved joint function and long-lasting clinical benefit[85].

5 y.o. TB gelding; 42 days; LFC Prox

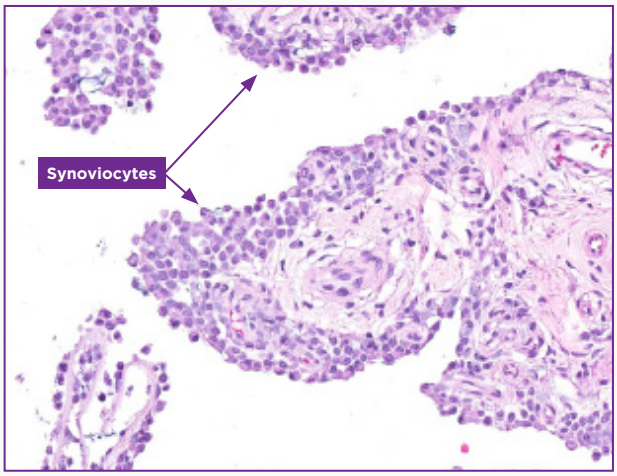


Figure 15. Higher magnification 42 days post injection showing establishment of a restored intimal cell layer 4-5 layers thick[85].

6.1 Clinical Safety

Most treatment options for OA focus on reducing symptoms rather than slowing or delaying the progression of the disease[12,23]. In addition, some treatments have been associated with significant adverse effects and contra-indications.

> Contura is committed to bringing medical devices and pharmaceuticals to market that meet applicable regulatory requirements and quality standards.

Therefore, the 2.5% iPAAG and the syringe used for storing and delivering the 2.5% iPAAG have been evaluated in a range of biocompatibility assays, and the clinical safety of Arthramid and other Contura products have been evaluated in a range of prospective and retrospective clinical studies.

The clinical safety of Arthramid is described below.



BIOCOMPATIBILITY

The Arthramid 2.5% iPAAG and the Arthramid syringe have passed an extensive variety of assays to document the safety and biocompatibility of the product.

This includes cytotoxicity, sensitization, irritation and intracutaneous reactivity, material mediated pyrogenicity, subacute and acute systemic toxicity, subchronic and chronic toxicity, implantation effects, reproduction and genotoxicity, carcinogenicity and neurotoxicity[105].

Based on these data, it can be concluded that when Arthramid is handled in accordance with the intended use, no harm or adverse events related to the biocompatibility of the product have been identified or reported.



PHYSICAL AND/OR CHEMICAL INFORMATION

A theoretical study evaluating the potential reactivity between polyacrylamide and constituents in the synovial fluid concluded that polyacrylamide molecules do not react chemically with any macromolecules present in synovial fluid[106].

Moreover, as part of the chemical characterization of Arthramid, studies have been executed to identify and relatively quantify compounds that can be extracted from the 2.5% iPAAG or the Arthramid syringe under exhaustive extraction conditions in alignment with ISO 10993-18:2020.

Based on the data obtained, it is concluded that no compounds are present in the hydrogel in concentrations high enough to pose a toxicological risk in humans or animals treated with the 2.5% iPAAG[107-111].

NEUROTOXICITY

Monomeric acrylamide (AM) is known to be neurotoxic whereas polyacrylamide is chemically inert and hence non-toxic.

Since the Contura 2.5% iPAAG contains trace amounts of AM the hydrogel has been studied in vitro using human stem cells-derived neurons to clarify whether it is neurotoxic.

It was concluded that the 2.5% iPAAG demonstrates no neurotoxic or cytotoxic effects at any tested time point (≤96 h) or concentration (≤20% v/v)[105].

In another study, the potential neurotoxicity of the hydrogel was investigated in vivo in a goat model of OA. In this study, the numbers and morphology of neurons located in the synovial membrane were assessed in response to treatment without or with the 2.5% iPAAG.

In both groups, neurons were intact with normal morphology, present in normal numbers, and with no indications of neurotoxicity[90]. This same finding was repeated recently in an equine model[95].

In conclusion, no in vitro or in vivo studies addressing the effects of the 2.5% iPAAG have produced data suggesting that the hydrogel is neurotoxic or possesses other types of toxicity.

6.2 In Vivo Safety Studies

The safety of Arthramid VICH GL43 guidelines: Ten individual horses received intra-articular injections at 1x ,2x and 3x the recommended dose rates and follow-up examinations were performed on days 1, 3, 7 and 14 after treatment.

Safety was evaluated using physical examination, including joint health and mobility, and evaluation of complete blood haematology, serum biochemistry and acute phase proteins (SAA).

The study demonstrates that intra-articular treatment of equines with 2.5% iPAAG is safe and with no adverse reactions or detrimental clinical effects, even at up to 3x the recommended dose[112].

LONG TERM SAFETY STUDIES

The safety of the product in vivo is further supported by a range of prospective and retrospective studies[70,84,90,96,99,101,113] including an investigation where medical records of 1,000 Warmblood horses over 10 years were analysed with only a single reported adverse event and that was not product-related[114].

In another long-term study of 701 Thoroughbred racehorses over 6 years receiving a total of 2,312 intra-articular injections, only 3 adverse events were reported (0.13%), and none were product related, compared to published rates of up to 0.02-0.08% with other intra-articular therapies[115,116].



7.1 Case Selection

Understanding the complexity of disease processes associated with joint pain remains a constant dilemma in clinical practice and, as with any disease process, an accurate diagnosis is essential.

> Arthritis describes inflammation of a joint and can occur after single or repetitive episodes of trauma.

The term incorporates synovitis, capsulitis, sprain, intra-articular fractures, meniscal tears and OA. Sub-chondral bone injury also plays a role.

Cases suitable for treatment with Arthramid are those in which lameness is localised to the joint by clinical examination, intra-articular analgesia, +/- radiography, ultrasound, MRI, CT and/or scintigraphy. Conditions that respond to treatment with Arthramid include acute and chronic synovitis, capsulitis, meniscal tears and OA.

It is essential that analysis of data of ongoing infection, concurrent medication, surgery or potential fracture is reviewed prior to injection to prevent possible infections or use of the product for conditions other than for which it is indicated.



7.2 Dose and Administration

Arthramid must be administered by a qualified veterinarian trained in intra-articular injections. It is administered via percutaneous infiltration into the articular cavity of the affected joint, delivering the required dose as advised depending on the joint being injected.

Recommended doses are listed below. The doses are based on observed clinical responses to administration. Concurrent treatment of multiple joints in the same animal is possible.

Joint	Dosage
Coffin [Distal interphalangeal]	**1-2 mL**
Pastern [Proximal interphalangeal]	**1 mL**
Fetlock [Metacarpophalangeal / metatarsophalangeal]	**2 mL**
Carpal	**2-3 mL**
Hock [Tarsometatarsal / distal intertarsal]	**1 mL**
Tarsocrural	**2-3 mL**
Shoulder [Scapulohumeral]	**2-3 mL**
Stifle [per compartment]	**2-3 mL**

7.3 Directions for Use

Arthramid should be administered in accordance with standard intra-articular injection procedure.

Sedate or restrain the animal according to normal practice. Thoroughly prepare the injection site with an aseptic preparation.

A sterile hypodermic needle (size 19-23G) should be placed intra-articularly. Synovial fluid should be observed. Ensure that the Luer lock is firmly attached to the Arthramid needle hub.

If more than 1 mL of Arthramid is required for the joint, detach the empty Arthramid syringe from the hypodermic needle and repeat the process until the required dose is delivered.

7.4 Post-Operative Procedures

Prophylactic non-steroidal anti-inflammatory drugs (NSAIDs) can be administered for pain relief.

Following treatment, the animal should be rested for 48-72 hours.

Training modifications to accommodate the degree of lameness and the disease process should be considered. e.g. 2 weeks rest or low impact exercise.

7.5 Complications

As with any intra-articular intervention, administration of Arthramid carries an inherent risk of infection, and strict adherence to aseptic technique is essential.

Reported adverse event rates associated with Arthramid are low[79,101,114,115].

However, transient local adverse reactions have been reported in a small proportion of treated animals (estimated <1:1500), typically manifesting as pain, heat or oedema at the injection site or within the treated joint.

These reactions may occur within hours to days following administration, and in some cases mild joint effusion or sensitivity may develop within the first 1–2 weeks.

In cases presenting with post-treatment joint inflammation, septic arthritis from improper injection technique must be considered and excluded as a priority, as this necessitates immediate and specific therapeutic intervention.

Once sepsis has been ruled out, most cases can then be attributed to a non-septic inflammatory response associated with hydrogel integration within the synovial environment.

Management of non-septic reactions is typically conservative and centred on anti-inflammatory therapy.

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally administered for 10–14 days, with adjunctive measures such as rest, cold therapy, and topical anti-inflammatory treatments providing additional clinical benefit.

In more pronounced cases, short-term antimicrobial therapy may be considered while sepsis is being excluded, and corticosteroids may be used to control an excessive inflammatory response.

Importantly, once sepsis has been excluded, further intra-articular interventions are typically contraindicated, as they may exacerbate the inflammatory response. Joint lavage should therefore be reserved for carefully selected severe acute cases where potential benefits outweigh the risk of perpetuating joint inflammation.

Where septic arthritis is confirmed, standard treatment protocols should be followed. Notably, Arthramid does not impair antibiotic penetration or promote bacterial sequestration within the joint.

Overall, non-septic inflammatory reactions are typically self-limiting, with resolution expected over several days to a few weeks under appropriate management.

Clinicians should allow up to 6 weeks for the full therapeutic effect of Arthramid to be realised before considering additional interventions.

No allergic reactions to Arthramid have been reported to date; however, ongoing pharmacovigilance remains essential.

Conclusions & Future Directions

Contura strives to improve the knowledge of Arthramid and several pre-clinical and clinical studies are in progress.

To be kept updated on new data regarding the safety or use of Arthramid please visit the Arthramid Contura website at: www.contura.com/animal-health/ or www.arthramid.com.

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