



Superior Quality,
Effective,
Safe:

ORTHOVISC®
Setting the standard for
osteoarthritis therapy

ORTHOVISC for osteoarthritis—

Less pain and improved mobility after just three injections

A study of the effectiveness of sodium hyaluronate in the treatment of knee osteoarthritis with ORTHOVISC showed a high degree of effectiveness in the treated joint after three intra-articular injections. Joint pain was significantly reduced and mobility (time to walk 50 feet) was improved (Figure 1).¹⁰

The benefits of viscosupplementation with ORTHOVISC in patients with moderate knee osteoarthritis were measured over a period of 27 weeks.

The safety profile of ORTHOVISC was similar to that observed with placebo, suggesting that adverse events were attributed to the injection, and not to the material injected.

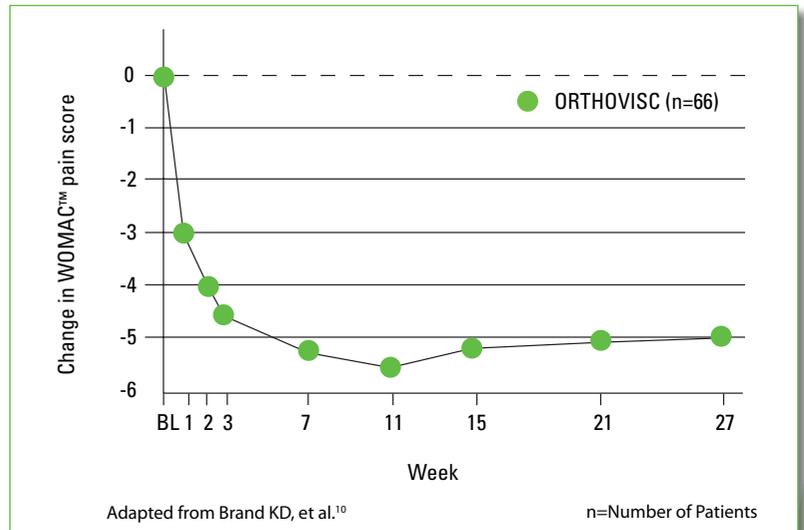


Figure 1. Therapeutic effect after three injections per treatment cycle with ORTHOVISC¹⁰

High molecular weight, high viscosity—optimal viscosupplementation

Normal joint fluid contains high concentrations of high molecular weight hyaluronan. ORTHOVISC, with high molecular weight hyaluronic acid and a high concentration of hyaluronic acid, delivers superior viscosity and cushioning for joint protection.

Exceptional purity and an exceptional safety profile

The exceptional purity of ORTHOVISC minimizes the risk of inflammatory reactions. In fact, no pseudoseptic reactions have been reported with ORTHOVISC.¹¹ ORTHOVISC is made from ultra-pure non-animal hyaluronan and is FDA-approved.[†]

Viscosupplementation with hyaluronic acid has been proven to be a safe, targeted therapy for osteoarthritis with minimal side effects. NSAIDs and analgesics can put the patient at risk of systemic side effects, and could also result in a progressive damage of the joint due to their focus on the reduction of stress-induced pain without additional viscous efficacy.

[†]ORTHOVISC is FDA-approved for use in the knee joint. ORTHOVISC is approved in the European Economic Area for use in all synovial joints.

Osteoarthritis and the concept of viscosupplementation

Know more, move more

The following pages summarize important information regarding the causes, forms and options for the treatment of osteoarthritis. Viscosupplementation with hyaluronic acid has been established as a sensible therapeutic option with few side effects. Also included is an introduction to the mechanism of action of this particularly beneficial treatment that is capable of alleviating arthritic discomfort and may slow the progression of the disease.

Osteoarthritis is a multi-symptomatic joint disease characterized by cartilage degeneration. Its rates of prevalence and incidence are closely correlated with age, gender and the serum level of hyaluronan.¹ Due to the increasing aging population in Western European countries and in the USA, the number of cases of osteoarthritis will increase significantly.

Osteoarthritis usually results in a restriction of the patient's quality of life. In addition to analgesic therapies, the focus has been on treatment modalities that save joint function. Decisions made regarding therapy selection must consider both the potential benefit and also the potential risks of each therapy.

Causes and characteristics of osteoarthritis

Causes of osteoarthritis may include those that are mechanical, traumatic, metabolic, post-inflammatory, genetic or age-related (Table 1).

Cause	Relevant Joints	Characteristics
Mechanical	Large joints	<ul style="list-style-type: none">• Scaling, surface damage, erosions and detaching of joint cartilage
Traumatic	Any joint	<ul style="list-style-type: none">• Initially only local damage• Adjacent cartilage may eventually be affected
Post-inflammatory	Any joint	<ul style="list-style-type: none">• Secondary osteoarthritis as a result of inflammatory joint processes• In end stage, hardly any distinguishing features compared with degenerative processes
Metabolic	Small joints	<ul style="list-style-type: none">• Deposits of urate crystals in cases of gout• Diseases of iron metabolism (hemochromatosis)
Genetic	Small or large joints	<ul style="list-style-type: none">• Polyarthroses of the fingers• Knee and hip osteoarthritis
Age	Large joints	<ul style="list-style-type: none">• Deficient cartilage growth without recognizable external causes

Table 1. Causes and locations of osteoarthritis

Forms of osteoarthritis and therapies

The most frequent form of osteoarthritis—occurring mostly in women in menopause—is polyarthrosis of the fingers followed by osteoarthritis of the knee and hip. It is estimated that approximately 5% of the world’s population suffer from arthritis of the knee. 30% of those over 50 years of age and 80% of those over 75 years develop this degenerative disease of the joints. Restricted mobility as a result of this disease can lead to considerable disability and the loss of the patient’s quality of life.

Treatment for osteoarthritis is multimodal and aims primarily to alleviate symptoms (Table 2). When selecting the method of therapy, potentially undesirable side effects—in particular when NSAIDs and analgesics are used—must be taken into consideration.

Surgical interventions are considered the “last resort” and are limited by the potential risk of surgery. Viscosupplementation with hyaluronic acid provides an additional drug-free and effective therapy which is recommended by medical associations for the management of knee osteoarthritis.²

Osteoarthritis Therapies	
Non-pharmacological therapy	<ul style="list-style-type: none">• Patient information• Physical therapy• Avoidance of stress factors• Orthopedic technology
Systemic pharmacotherapies	<ul style="list-style-type: none">• Analgesics• NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)• Glucosamine sulfate
Local pharmacotherapies	<ul style="list-style-type: none">• Intra-articular injection of corticosteroids• Intra-articular injection of hyaluronic acid
Surgical therapies	<ul style="list-style-type: none">• Repositioning osteotomies• Arthrodesis• Joint replacement procedures

Table 2. Osteoarthritis therapy modalities

Function of hyaluronic acid in cartilage

Hyaline cartilage consists of chondrocytes embedded in an extracellular matrix (Figure 2, Figure 3). This matrix is composed of a fibrous network containing a Type-II collagen and of proteoglycans and glycosaminoglycans present between the fibers.

Glycosaminoglycans consist of hyaluronans (hyaluronic acid), chondroitin sulfate and keratane sulfate. These hyaluronans consist of units of N-acetylglucosamine molecules and sodium glucuronate molecules in polysaccharide chains and may have molecular weights of up to 1.0×10^7 daltons following polymerization.³ They are primarily responsible for the elasticity and buffering capability of cartilage in that they are released in the interstices of collagen fibers as well as in the joint itself and in its capsule. The high viscosity and thus the elasticity of the hyaluronans is mainly due to their polysaccharide character. Normal synovial fluid contains high concentrations of hyaluronan (2.5-4.0 mg/mL).



Figure 2.
Normal knee joint

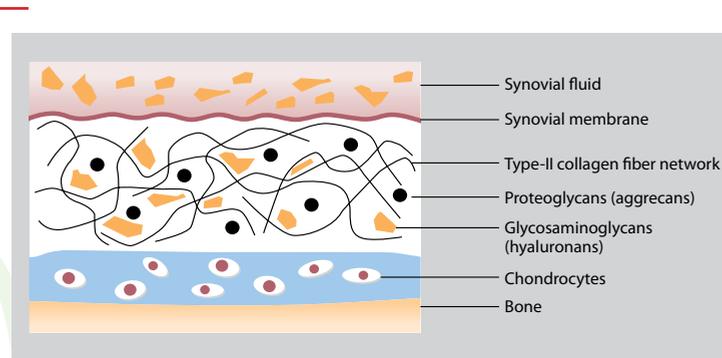


Figure 3.
Knee joint surface with cartilage layer



Figure 4.
Knee joint with signs of osteoarthritis

Because of their high water-binding capacity, hyaluronans can dampen numerous physical stress factors acting on the joint. With low stress on the joint, the hydrophilic molecule exhibits high viscosity and low elasticity due to water-binding. However, if high pressure acts on the joint, the molecule—primarily due to the absorption of water—has an extremely elastic effect. For example, the same molecule may perform a lubricating function at low stress or act as a buffer/shock absorber under high stress. In synovial fluid, this function is exclusively performed by the hyaluronans.

The cartilage-specific proteoglycan aggrecan is also responsible for the structure of the cartilage matrix. Aggrecan inhibition, for example by aggrecanases, results in the erosion and loss of the cartilage.

Osteoarthritis causes the proteoglycans and hyaluronans to lose their physicochemical properties. Due to the influence of synthetases facilitated by cytokines, a reduction of the molecular weight of the hyaluronans to below 0.5×10^6 daltons occurs, the concentration of the hyaluronans decreases and so does their elasticity and viscosity.⁴ As a result, the support and nutrient function of the cartilage matrix is disrupted. Finally, disruptions of the balance of the matrix can also lead to a damage of the deeper layers of the chondrocytes and even to the bone itself (Figure 4).

Viscosupplementation as a therapeutic concept for the treatment of osteoarthritis

Viscosupplementation has proven to be an effective therapy in cases of degenerative arthritic changes in the joints.^{8,9,10} The principle of viscosupplementation is based on the use of intra-articular injections of hyaluronans.

The primary and immediate benefit of viscosupplementation with hyaluronan is the replacement of synovial fluid. The goal is to improve the viscoelasticity of the synovial fluid, allowing it to function as a viscous lubricant or an elastic material under varying load conditions and mechanical stresses. The injection of hyaluronan into the joint space results in both the reduction of pain and improved mobility in the treated joints.

The viscoelasticity of synovial fluid is determined by both the concentration and the molecular weight of its hyaluronan component.⁸ Available hyaluronic acid (HA) preparations vary in their HA concentration, molecular weight and viscosity (Table 3).

Product	HA Concentration (mg/mL)	Molecular Weight (million daltons)	Viscosity (Pa at 2.5 Hz)
ORTHOVISC	15	1.45	45
Product B	8 (hylan A only)	3.09	33
Product C	10	1.25	5.19
Product D	10	.66	.53
Product E	10	.57	.37

Table 3. Viscosupplement property comparisons¹²

A number of studies have shown increased efficacy, analgesia and patient satisfaction with high molecular weight supplements.^{5,6,7} After only three injections, a preparation with a higher molecular weight may provide long-term freedom from pain over a period of six months.^{9,10}

Hyaluronic acid therapies with a low molecular weight can require a treatment regimen of five injections into the affected joint,¹³ increasing the risk of infection in the treated joint. Therapies with a higher molecular weight require fewer injections per treatment cycle and thus appear to involve a lower risk of infection.

In addition to the mechanical effects of viscosupplementation, therapeutic biological effects may also be present. Based on experimental studies, there are indications that the intra-articularly administered hyaluronans also have a positive effect on the damaged cartilage matrix.^{3,5,6}

setting the standard for viscosupplementation

Effective

- Reduces pain in the joint¹⁰
- Improves patient mobility¹⁰
- Results with just 3 injections per treatment cycle¹⁰
- Long-lasting efficacy¹⁰

Superior Properties

- High hyaluronic acid concentration of 15 mg/mL
- Ideal molecular weight averaging 1.9×10^6 daltons
- Optimal dynamic viscosity provides improved elasticity to synovial fluid

Safe

- High degree of purity
- No pseudoseptic reactions in more than 6 million injections worldwide¹¹
- Production by fermentation process eliminates the risk of allergic reactions to animal proteins

References

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- ¹¹ Anika product analysis data on file, 2013.
- ¹² Sadozai KK. Evaluation of the characteristics of sodium hyaluronate products used for treatment of osteoarthritis. 2006. Data on file at Anika Therapeutics, Inc.
- ¹³ Hyalgan Instructions for Use, Ostenil Instructions for Use.

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Fermented Source Sodium Hyaluronate



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