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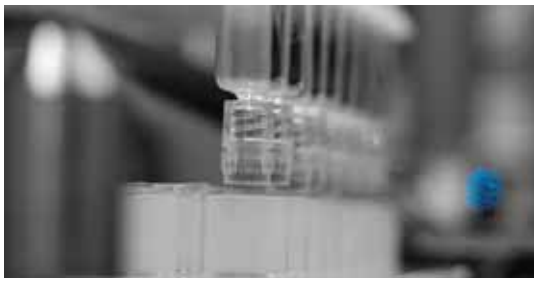


ORTHOFLEX ®
Medical Report

Quality products.

Orthoflex one is produced according to Good Manufacturing Practice (GMP) and ISO13485 being certified as a system with high quality ingredients, CE marked medical device being in accordance with the European Directive 93/42/EE.

Advanced Technology

The manufacturing in compliance with Romanian law no 95/2006 regarding medicines for human use. Valid Manufacturing Authorization, in full compliance with GMP issued by the National Medicine and Medical Devices Agency.
Manufacturing operations for investigational medicinal products include total or partial, certification and batch release, import, storage and distribution and tests (microbiological and physical-chemical) for quality control.

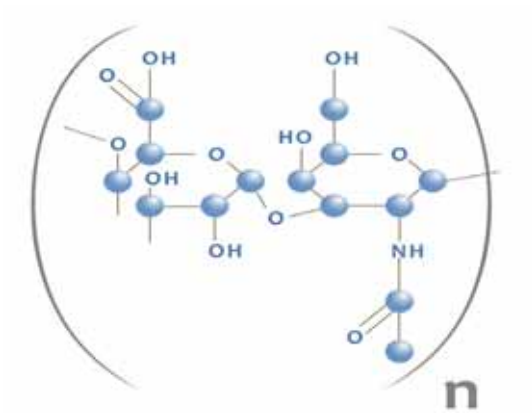
Medical investigation, approved result.

ORTOBRAND has a method that is currently unique with regard to the combination of its advantages. The raw material selected according to the highest quality aspects is cross-linked in a special way. The products are thus particularly stable in the human

body. Natural enzymatic degradation processes are slowed down by the cross-linked and gel-like substance, and by the associated reduction in the molecule surface of the products. Processes are slowed down by the cross-linked and gel-like substance, and by the associated.

The extraction of hyaluronic acid (non-animal origin) through biofermentation also reduces the likelihood of immune responses to a minimum. ORTOBRAND products have an optimized injection behavior that is reflected in the of the hyaluronic acid from ORTOBRAND.

SODIUM HYALURONATE



- Hyaluronan (also known as sodium hyaluronate or hyaluronic acid) is a natural and linear glycosaminoglycan, and is ubiquitous in all the tissues and fluids of animals, with the highest concentrations in soft connective tissues.
- In 1934, Karl Meyer and his assistant John Palmer first announced the discovery of HA. They purified HA from bovine vitreous and showed that it contained a hexuronic acid and a hexosamine. They proposed "for convenience, the name hyaluronic acid, from hyaloid (vitreous) + uronic acid." Up to the mid-1940s, HA had been isolated successfully from other sources- synovial fluid, skin, umbilical cord, cock's comb, etc.
- In 1980s, Dr. Endre Balazs and his coworkers developed a procedure to isolate, purify and identify hyaluronic acid from rooster combs and human umbilical cords. Since then, HA has been produced at industrial scale from rooster combs and human umbilical cords.
- Discovered from bacteria.It is known that the capsules of some bacteria contain HA, therefore, HA can also be isolated from certain strains of bacteria, such as streptococci, which was first reported in 1937 by Kendall et al. They cultured Group A streptococci and then the mucoid polysaccharide was precipitated with ethanol. This polysaccharide which was composed of N-acetyl glucosamine and glucuronic acid units was identical with that occurring in bovine vitreous humor and human umbilical cord. The bacterial production of HA involving a Streptococcus zooepidernicus strain was first described in 1989, giving rise to the first commercialization of HA produced by fermentation.
- By the end of the 20th century, bacterial fermentation had become the leading production technique for sodium hyaluronate, and it has led to great changes in the sodium hyaluronate industry. The industry is now able to produce a higher quality HA product on an industrial scale necessary to support the continued expansion of HA applications into new areas of science. The techniques have also lowered the cost of HA production to a point that has allowed many applications to go mainstream that might have proved too costly for markets previously.
- Commercial HA is commonly presented as the form of sodium salt.
- During the manufacture of HA, sodium salts (such as sodium chloride or sodium hydroxide) are often used to increase ionic strength or to adjust pH value, therefore, most of HA products is presented as the form of sodium salt, named sodium hyaluronate.

Joint Pain and Arthritis

With overuse or injury, cartilage on the end of the joints can break down, causing a narrowing of the joint space and the bones to rub together. Painful bony growths, or spurs, may form. This can lead to swelling, stiffness, and possibly osteoarthritis, the most common type of arthritis. Another type of arthritis is rheumatoid arthritis, an auto-immune disease characterized by extreme inflammation.

What is Osteoarthritis?

- Osteoarthritis is a disease that affect the joints in your body.
- While it can affect any joint , osteoarthritis most commonly in the hands , hip, Knees, neck and lower back.
- Osteoarthritis (OA) is the most common joint disease and cause of disabilities, especially in the elder people (more than 80 percent of the population over 55 years of age is affected by osteoarthritis).
- Also known as degenerative arthritis, de-generative joint disease or OA, it occurs when the cartilage that normally covers and cushions the ends of bones wears down over time. It is characterized by cartilage erosion, changes in subchondral bone, osteophyte formation and synovial inflammation.
- The main symptoms of OA are chronic pain, stiffness and loss of mobility.

How does OA develops?

Osteoarthritis is caused by cartilage resulting in a joint pain.

- The smooth cartilage surface wear down. Then this happens, the cartilage loses its elas-ticity and more easily damage by excess use or injury.
- With time section of cartilage may wear away completely. As a result the bone rub together.
- As the cartilage wear down , the join may lose its normal shape. The bone end thicken. The bone at the edge of the joint mat grown outward and form body spurs.
- Fluid – filled cysts may form in the bone near the joint . Bit of bone or cartilage may float loosely in the joint space.

Osteoarthritis of the Knee

When osteoarthritic joints became swollen and damaged , they can be painful and difficult to move.

- If you have OA of the knee the symptoms pain, stiffness limited range of motion.
- In the arthritic joints , the normal concentra-tion and molecular weight of hyaluronate (HA) is decreased by 33% to 50%, limiting its role in maintaining normal joint biomechanics.

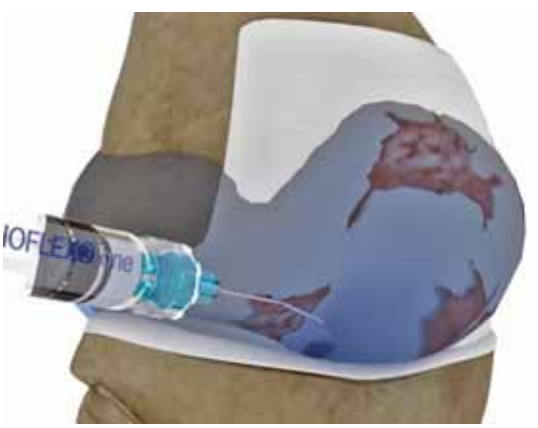
VISCOSUPPLEMENTATION

What is Viscosupplementation?

- Viscosupplementation refers to a procedure that involves the use of HA solution to supplement or replace synovial fluid in joint with pathological conditions to alleviate pain and promote the healing of intra-articular wounds. The viscosupplementation should improve the physiological environment of an osteoarthritic joint by restore the protective viscoelasticity of synovial fluid, reduce friction, and improve mobility.
- Studies have confirmed the satisfactory effect of HA to treat lameness in race horses and osteoarthritis (OA) in human knees, hips, shoulders, and temporo-mandibular joint, and so forth. The use of HA solution in OA treatment is considered to be the most successful medical applications of HA.
- Viscosupplementation has as its therapeutic goal the restoration of rheological homeostasis in pathological structures such as osteoarthritic joints. When the normal viscoelasticity of a solid tissue compartment or the elastoviscosity of a liquid tissue compartment is decreased under pathological conditions, normal function and regenerative processes are impaired. By introducing viscosupplementary devices, the normal rheological state of such compartments is restored or augmented. These devices stay in the tissue compartment for various periods of time, depending on the nature of the viscosupplement and the pathophysiology of the tissue compartment.

Mechanism of action

- Viscosupplimentation with HA has various mechanism of actions on the osteoarthritic knee. In addition to repletion of intra -articular HA and its viscous and elastic properties , HA also have anti inflammatory, anabolic and analgesic properties.
- HA has been identified as the molecule responsible for imbuing the knee with this rheostatic properties. HA is polysaccharide chain composed of repeating disaccharide units of glucuronic acid and N –acetylglucosamine. HA is normally synthesized by tipe B synoviocytes or fibroblasts and is secreted into the joints. In the osteoarthritic knee the concentration of HA is decresed to nearly one half of normal, the MW is reduced (as polysaccharide chains are cleaved) and this is decreased interaction between HA molecules. These changes after the inherent viscous and elastic properties of HA and reduces the ability of the joint to resist stress and shear forces.
- HA is viscoelastic substance because it exhibits both viscous and elastic properties. This allows the joint optimally adapt to different externally applied forces. The knee experiences low shear loads during simple range of motion. Under these conditions , viscous properties predominate and the HA molecules line up and act as a lubricants . under high shear loads , HA molecules behave and an elastic substance and absorb energy that is transmitted across the joint.
- Because native HA is decreased in the osteoarthritic knee and HA restores these lost viscoelastic properties , descriptions of these product as viscosupplements seems reasonable .



ORTHOFLEX ® one

Natural cross linked hyaluronate. The only single injection.

Prefilled syringes

Natural Cross-linked Hyaluronate 60 mg + Chondroitin Sulfate 90mg / 3ml

A new generation of viscosupplements

Description

- ORTHOFLEX one® is single treatment , viscoelastic gel injectable prefilled syringe used intra articular for treating arthritis. It is similar to synovial fluid, a substance that occurs naturally in the joints, synovial fluid acts as a lubricant and shock absorber.
- ORTHOFLEX one® is cross~linked hyaluronate 60mg/3ml solution of highly purified sodium hyaluronate + chondroitin sulfate 90mg/3ml, with high molecular weight that guarantees its excellent efficiency and a strong therapeutic effect (3,0 million daltons).
- Obtained by bio fermentative process, synthetic origin gives a complete safety eliminating any allergic reactions.
- ORTHOFLEX one® is a prefilled syringes having aluminum blister for sealing that assure 3 years guarantee of validity , sterilized by autoclave.Effects

Chondroitin Sulfate and Hyaluronic Acid with ORTHOFLEX one® in the treatment of degenerative joint disease.

- Hyaluronan contributes to the synovial fluid's lubricating properties and also controls fluid flow into and out of the joint space.
- Injected into knee joints with osteoarthritis (OA) to ease pain and stiffness. Chondroitin sulfate, is a structural component of aggrecan in cartilage and provides much of its resistance to compression.
- Chondroitin sulfate (CS) and hyaluronic acid (HA) induces cartilage destruction and acts as a mediator of the inflammatory response.
- Using Chondroitine Sulfate as a cross-linking agent increase biocompatibility and biodegradability native polymer and creates premises delay of cartilage degeneration and even supports regeneration cartilage structure.
- ORTHOFLEX one® –improved by cross linking , preponderantly elastic, confers capacity mechanic protection increased and improved lubrication(≥45Pa characteristic human synovial fluid).

Indications

The treatment consists in administration of intra-articular single treatment :

- ORTHOFLEX one® is indicated for the symptomatic treatment of mild of severe osteoarthritis.
- Orthoflex one is recommended for patients that have joints pain coupled with reduced mobility. These symptoms can occur as a result of degenerative disease or trauma.
- ORTHOFLEX one® treats pain and restricted mobility and elasticity , protect cartilage as a result of traumatic pathology in the knee joint and other synovial joints(hip, ankle, shoulder, elbow, wrist, fingers, toes, and the temporomandibular and facet joints)
- Is also indicated for the reduction of post–arthroscopy pain.
- Is contraindicated in children, pregnant or breast–feeding women.

What Is Chondroitin Sulfate?

- Chondroitin Sulfate is a molecule, which occurs naturally in the body. It is an important component of cartilage - the tough connective tissue that cushions the joints.

How Does It Work?

- The functions of chondroitin sulfate: It delivers nutrients to the joint cartilage, helps to inhibit the enzymes that decompose the joint cartilage and speeds up the formation of a new joint cartilage. the elasticity and plasticity, which are the functions of the joint cartilage can be maintained through the use of Chondroitin Sulfate.

Why Use Chondroitin Sulfate?

- Chondroitin Sulfate is widely used in the treatment of osteoarthritis
- It can also block the enzymes that degrade cartilage, and it provides the building blocks for the body to produce new cartilage.
- Chondroitin Sulfate appears to be very important in keeping joints healthy by means of its unique ability called chondro protection, retention or stimulation of repair function in cartilage cells.
- The body needs nourishment to heal and repair itself and Chondroitin Sulfate has been proven to stimulate the growth of new joint cartilage it is now considered an essential substance for the maintenance of healthy joints.

Physicochemical Properties:

The treatment consists in administration of intra-articular single treatment :

- Treatment 1injection
- 60mg/3ml (2%) sodium hyaluronate
- 90mg/3ml chondroitin sulfate
- Average molecular weight 3 million Daltons (viscometric data)
- Elasticity minimum 110 Pa (2.5Hz, maximum effort)
- Viscosity minimum 45 Pa (2.5Hz, maximum effort)

ORTHOFLEX ® forte

Protect cartilage and greatly improve the joints mobility.

Prefilled syringes

Sodium Hyaluronate 30 mg/2ml

Synovial fluid supplement

Description

- ORTHOFLEX forte® is a viscoelastic injectable prefilled syringe used intra articular for treating arthritis. It is similar to synovial fluid, a substance that occurs naturally in the joints, synovial fluid acts as a lubricant and shock absorber.
- ORTHOFLEX forte® is 30mg/2ml solution of highly purified sodium hyaluronate with high molecular weight that guarantees its excellent efficiency and a strong therapeutic effect (2,0-2,9 million daltons).
- Obtained by bio fermentative process, synthetic origin gives a complete safety eliminating any allergic reactions.
- ORTHOFLEX forte® is a prefilled syringes having aluminum blister for sealing that assure 3 years guarantee of validity, sterilized by autoclaving.

Effects

- ORTHOFLEX forte® has in the medium term, a double effect by restoring in the joints the levels of sodium hyaluronate, restoring also the mechanical properties of synovial fluid and having a long-lasting effect by stimulating naturally the body in secretion of hyaluronic acid. The therapeutic efficacy has been proved up to six months of relief, replaces natural joint fluid to cushion, protect and lubricate the knee, help restore mobility by treating knee pain at its source.

Indications

- ORTHOFLEX forte® is recommended for patients that have joints pain coupled with reduced mobility. These symptoms can occur as a result of degenerative disease or trauma.
- ORTHOFLEX forte® greatly reduces pain, treating and restoring joint mobility and elasticity.
- The treatment consists in administration of intra articular injections between 1 - 3 ORTHOFLEX forte®/1 at weekly intervals depending on the severity of the degenerative or traumatic change to the synovial joint.
- Indications like Gonarthritis, Coxarthritis, Omarthritis, Arthritis of the elbow, Rhizarthritis and Ankle arthritis.

Physicochemical Properties:

- Treatment 1-3 injection
- 30mg/2ml (1.5%) sodium hyaluronate
- Estimative molecular weight sized into 2.0÷2.9 million Daltons (viscometric data)
- Average molecular weight 2.4 million Daltons(viscometric data)
- Intrinsic viscosity 1.5 – 3.8m3/kg
- Osmolarity300 - 370 mOsmol/kg
- Endotoxin limit -less than 0.5 EU/mg sodium hyaluronate
- PH 5.0- 8.5
- Elasticity minimum 60 Pa (2.5Hz, maximum effort)
- Viscosity minimum 45 Pa (2.5Hz, maximum effort)

Quality

- ORTHOFLEX forte® is produced according to Good Manufacturing Practice (GMP) and ISO13485 being certified as a system with high quality ingredients, CE marked medical device being in accordance with the European Directive 93/42/EE.

ORTHOFLEX ® tendon

Restore mobility in damaged tendon.

Prefilled syringes

Sodium Hyaluronate 40 mg/2ml + 10mg mannitol

Number one in sprained ankle treatment

Description

- ORTHOFLEX forte® is a viscoelastic injectable prefilled syringe used intra articular for treating arthritis. It is similar to synovial fluid, a substance that occurs naturally in the joints, synovial fluid acts as a lubricant and shock absorber.
- ORTHOFLEX forte® is 30mg/2ml solution of highly purified sodium hyaluronate with high molecular weight that guarantees its excellent efficiency and a strong therapeutic effect (2,0-2,9 million daltons).
- Obtained by bio fermentative process, synthetic origin gives a complete safety eliminating any allergic reactions.
- ORTHOFLEX forte® is a prefilled syringes having aluminum blister for sealing that assure 3 years guarantee of validity, sterilized by autoclaving.

ORTHOFLEX tendon® is injectable prefilled syringe 40mg/2ml natural solution of highly purified sodium hyaluronate obtained by biofermentation devoid of animal protein + 10 mg mannitol , a free radical scavenger which help to stabilize the chains of sodium hyaluronate.

Effects

Acts as a lubricant when applied into the tendon sheath or peritendinously.

- Enhance tendon gliding effect and reduce adhesion.
- Prevents the free passage of inflammatory cell and molecules through the tendon sheath due to its macromolecular meshwork.
- Promotes tendon recovery and would healing process.

Precautions

- ORTHOFLEX tendon® should be instilled accurately into tendon sheath or around the affected tendon if necessary under imaging control, avoid nerve lesions and injections into blood vessels.

Indications

- For the treatment of pain and restricted mobility in tendon disorders.
- Ankle and Foot
  - * achilles tendinopathy
  - * posterior tibial tendinopathy
  - * peroneal tendinopaty
- Shoulder- rotator cuff tendinopathy
- Elbow- lateral and medial epicondylalgia
- Knee – patellar tendinopathy

ORTHOFLEX tendon® should be administred once a week for total of 2 injections.

Characteristics:

- Treatment of tendon disorders
- 2 ml prefilled syringe for single use
- Sodium hyaluronate 2%(40mg/2ml)+ mannitol(10mg)
- Molecular weight- 3000kDa
- Duration on effects – 6 month

Quality

- ORTHOFLEX tendon® is produced according to Good Manufacturing Practice (GMP) and ISO13485 being certified as a system with high quality ingredients, CE marked medical device being in accordance with the European Directive 93/42/EE.

How to use ORTHOFLEX ®

HOW TO USE ORTHOFLEX ® one and ORTHOFLEX ® forte

Injection

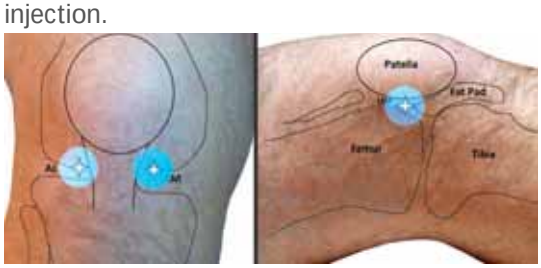
- The affected knee is first aspirated to remove any effusion that may be present, decreasing the concentration of inflammatory mediators that may be present and limiting the dilution effect the effusion would have on the injected material.
- Superolateral or lateral midpatellar injection site is the most reliable for reaching the synovial joint space of the knee.

Method of administration and dosage

- ORTHOFLEX ® one and ORTHOFLEX ® forte is administered only by medical professionals trained for Intra -articular administration technique.
- ORTHOFLEX ® one and ORTHOFLEX ® forte must be administered strictly intra- articular.
- Do not administer intravenously.
- The volume will vary depending upon the size of the joint space , not to exceed 2ml for the knee and other large joints or 1ml for small joints.
- It is the physician's responsibility to determine the appropriate volume and ensure that the joint is not overfilled.
- ORTHOFLEX ® forte is administered in the affected joint once a week for 3 consecutive weeks.
- Several joints may be treated simultaneously.
- Not to exceed one treatment course for any individual joint in any 6- month periods.
- Any joint effusion present should be removed by joint aspiration before injecting ORTHOFLEX ® forte.

The intra -articular space should not be overfilled.

- ORTHOFLEX ® one and ORTHOFLEX ® forte is available as a ready to use pre-filled syringe and must not be diluted. The content of a pre-filled syringe ORTHOFLEX ® is sterile and must be used immediately after the packaging has been opened.
- ORTHOFLEX ® one and ORTHOFLEX ® forte should be injected slowly into the joint space using a standard intra – articular injections technique.
- Remove the pre-filled syringe from the package. Before administration break the visible seal and remove the cap of the pre-filled syringe. Attach the hypodermic needle and make sure you have it properly fixed by turning it slightly.
- Remove the air from syringe before the injection.



Precautions

- General precautions should be observed for the intra-articular injection administration. Sodium hyaluronate should be administered in the synovial space only by medical professionals trained in intra-articular administration technique.
- An excess amount of sodium hyaluronate is not to be used and the patient should be monitored closely. The intra- articular space should not be overfilled.
- If pain increase during the injection procedure, the injection should be stopped and the needle withdrawn.
- Patient should be carefully examined prior to administration to determine signs of acute inflammation and the physician should evaluate whether Orthoflex forte treatment should be initiated in this case. As in any invasive joint procedure it is recommended caution to avoid over using the joint immediately after the intra-articular injection. To date, there are insufficient data to recommend the use in children and adolescents. Orthoflex forte should not be intra- articularly administered simultaneously or mixed with other products.

HOW TO USE ORTHOFLEX ® tendon

- Inject ORTHOFLEX ® tendon around the affected tendon once a week for a total of two injections. Several tendons can be treated simultaneously. Repeat treatment as needed.
- The content and outer layer of the ORTHOFLEX ® tendon syringe is sterile, provided that the packaging has not been opened or damaged. Remove the prefilled syringe from the packaging, unscrew the Luer-Lok, attach a suitable needle (for example, 25-27 G), and twist to secure.
- Remove all air bubbles prior to injection.
- ORTHOFLEX ® tendon should be instilled accurately into the tendon sheath or around the affected tendon, if necessary under imaging control. Avoid nerve lesions and injections into blood vessels!