**Presentation:**

For the relief of the symptoms of osteoarthritis of the knee by providing support and lubrication to the knee joint.

**RenehaVis™** is two clear solutions of sterile sodium hyaluronate in a phosphate buffered saline contained in a two chamber pre-filled syringe for single intra-articular injection into the synovial space of the joint.

**RenehaVis™** 0.7ml LMW and 0.7ml HMW, terminally sterilised by moist heat, is enclosed within a glass, ready to use, disposable syringe. The syringe is packed within a blister pack and an outer cardboard carton.

**RenehaVis™** is a sterile pre-filled two-chamber glass ready to use disposable syringe containing:

**Chamber 1**

Sodium hyaluronate Low Molecular Weight (LMW): 0.7ml sterile 2.2% sodium hyaluronate $1x10^6$ Da molecular weight.

**Chamber 2**

Sodium hyaluronate High Molecular Weight (HMW): 0.7ml sterile 1.0% sodium hyaluronate $2x10^6$ Da molecular weight.

**LMW Sodium hyaluronate 15.4mg/0.7ml**

**HMW Sodium hyaluronate 7.0mg/0.7ml**

**Dosage and Administration:**

Injection of **RenehaVis™** should only be made by a Healthcare Professional trained in the technique.

The dosage regimen is injection into the affected synovial joint space once a week for up to three injections depending on the severity of the degenerative change to the knee joint.

Clean the skin around the injection site with antiseptic and allow to dry before injection is given.

If joint effusion is present it should be aspirated before injection of **RenehaVis™**.

The contents of the syringe are sterile and should be injected using a sterile needle of an appropriate size (25 gauge needle is recommended). The syringe is fitted with a Luer lock (6%).

Discard the syringe and needle after single use.

**Uses:**

For the relief of pain and stiffness of the knee joint in patients with degenerative changes to the synovial joint. The duration of effect in patients with grade 1 to 3 medial compartment osteoarthritis has been demonstrated to be up to four months.

The performance of **RenehaVis™** is due to its biocompatibility and physicochemical properties. The LMW and HMW sodium hyaluronate contained in **RenehaVis™** is a biopolymer composed of repeating disaccharide units of N-acetylglucosamine and glucuronic acid and though it is biosynthesised by the bacterium Streptococcus equi it has been shown to be the same as the sodium hyaluronate which is found in the human body. **RenehaVis™** supplements the endogenous Sodium Hyaluronate found naturally in the synovium but which has been depleted by degenerative and traumatic changes to the synovial joint.

**Contra-indications:**

Do not inject **RenehaVis™** if the area of the injection is infected or where there is evidence of skin disease.
Patients with known sensitivity to sodium hyaluronate.

**Warnings and Precautions:**

Do not use if packaging has been damaged. Do not use after the expiry date.

Sodium hyaluronate is manufactured by fermentation of Streptococcus equi and rigorously purified. However, the physician should consider the immunological and potential risks that can be associated with the injection of any biological material.

Do not use for children.

Follow national or local guidelines for the safe use and disposal of needles. Obtain prompt medical attention if injury occurs.

**Adverse Reactions:**

Transient pain and swelling may occur with intra-articular injections. Transient increases in inflammation in the injected synovial joint following injection of **RenehaVis™** may occur in patients with inflammatory osteoarthritis.

Rarely an inflammatory reaction could occur which may or may not be associated with **RenehaVis™**.

**Incompatibilities:**

**RenehaVis™** has not been tested for compatibility with other substances for intra-articular injection. Therefore the mixing or simultaneous administration with other intra-articular injectable is not recommended.

**Storage:**

Store between 2°C and 25°C. Do not freeze. Protect from light.
Do not use if sterile packaging has been damaged.
Sterile product for single use only.
Do not use after expiry date.


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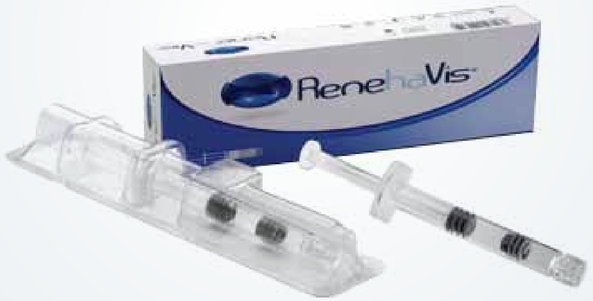
RenehaVis™
For knees dynamic needs





MDT Int'l s.a.
Geneva - Switzerland
www.mdtint.com


**Back Cover**

RenehaVis™
For knees dynamic needs

**Patent Combinations of**
**High Molecular Weight +**
**Low molecular weight**
**Hyaluronic Acid Derivative**

PATENT COMBINATIONS

## OBTAINED BY BIOFERMENTATION

- No animal origin, so no allergy
- No chemically modified agents, so no cytotoxicity
- Single Injection
- Two Molecular Weights
- Two Concentrations

**Cover**

## RenehaVis™ - THE DUAL CHAMBERED SYRINGE

### Physical changes in Knee Joint with OA

- Reduction of joint space
- Death of chondrocytes (cells living in cartilages)
- Loss of lubrication
- Loss of shock absorption

### RenehaVis™

- Increases level of endogenous HA within osteoarthritic joint
- Delays progression of cartilage degradation and bone deterioration
- Increases mobility and independence


**Chamber 1**

**1,000 KDa HA (AMW)**

- ✔ **Lubrication**
- ✔ Activate MSS
- ✔ Caging Effects

**2.2% concentration**

- ✔ **Protect chondrocytes**
- ✔ Stimulate synoviocytes
- ✔ **Lubricant**

**Chamber 2**

**2,000 KDa HA (AMW)**

- ✔ **Shock absorber**
- ✔ Reduce friction
- ✔ Protect Cartilage

**1.0% concentration**

- ✔ Temporary cushion to prevent further deterioration of joint
- ✔ Stimulate synoviocytes
- ✔ Lubricant

### Low molecular weight HA

- Responsible for Joint space
- Protects chondrocytes
- Acts as lubricants

### High molecular weight HA

- Acts as shock absorber

## KNEE PHYSIOLOGY

**Cartilage**

**Lubrication**

- HA production is consistently maintained
- Balance between synthesis and degradation of HA

**Caging Effect**

- Chondrocytes are the only matrix factory
- Chondrocytes are healthy and protected for continuous HA synthesis

**Synovial membrane + Synoviocytes**

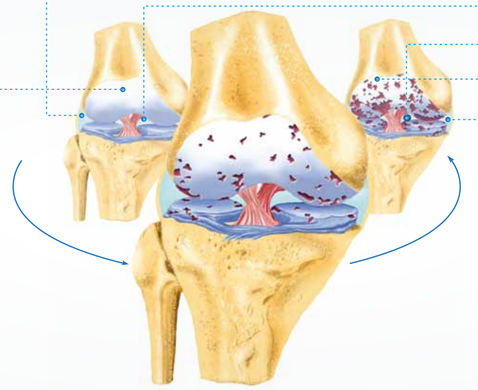
**Mechano-Sensitive Stimulation (MSS)**

- Concentration and Molecular Weight dependent
- Production of HA is rapid when stimulated by stretching of the synovial membrane

**Synovial Fluid**

**Viscoelastic properties**

- High content of HA in synovial fluid
- Provides shock absorption and lubrication
- Prevents friction
- Prevents damage to cartilage during activities
- Nourishes chondrocytes



**Cartilage**

**Degradation**

- Cartilage layer is significantly thinner
- Decreased number of chondrocytes due to lack of protection
- Significant decrease in HA production
- Bone becomes exposed and begin to deteriorate resulting in pain and reduction in mobility

**Reduction in Mechano-Sensitive Stimulation**

**Mechano-Sensitive Stimulation (MSS)**

- Synovial membrane is compressed
- Synoviocytes are less stimulated
- Reduction of HA production

**Synovial Fluid**

**Viscoelastic properties**

- Reduction of shock absorption and lubrication – overall loss in viscoelastic properties

## OSTEOARTHRITIS PATHOPHYSIOLOGY

## PHYSIOLOGICAL EFFECTS OF EXOGENOUS HA

**LMW HA + CARTILAGE + SAPLs**

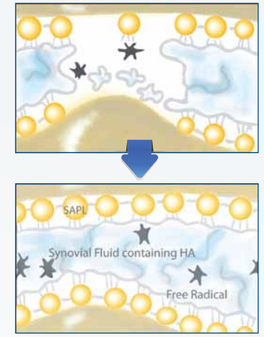
**LMW HA**

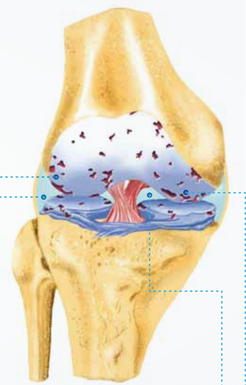
- Diffuses to cartilage layer
- Enhances and maintains the lubrication on the cartilage layer
- Protects SAPLs (Surface Active Phospholipids) from being degraded by free radicals.

**LMW HA + Synovial Membrane + Synoviocytes**

**Induces Mechano-Sensitive Stimulation**

- Increases volume of HA in synovial fluid
- Increases hydrodynamic volume in synovial joint
- Increases endogenous HA production further



**RenehaVis™**
GIVES LONG LASTING EFFECTS

**LMW HA + CARTILAGE + Proteoglycans + Chondrocytes**

**LMW HA**

- Diffuses to cartilage layer
- Increases production of endogenous HA
- Forms a protective cage around chondrocytes
- Reduces chondrocytes apoptosis
- Acts as backbone for proteoglycans

**LMW HA + Synovial Fluid**

**LMW HA**

- Increases synovial fluid's viscoelastic properties
- Increases shock absorption
- Restores synovial joint space
- Decreases rate of deterioration of cartilage and of bone

## PHYSIOLOGICAL EFFECTS OF EXOGENOUS HA