CombiMAX

INSTRUCTIONS FOR USE

CE 0050

CombiMAX

Sodium hyaluronate 36 mg/2.25 ml, chondroitin sodium sulfate 67.5 mg/2.25 ml and N-acetylglucosamine 67.5 mg/2.25 ml, solution for injection in pre-filled syringe.

For intra-articular injection

DESCRIPTION:
CombiMAX is a bio-matrix in the form of a sterile, viscoelastic solution consisting of two highly purified cross-linked biopolymers, sodium hyaluronate and chondroitin sodium sulfate, and N-acetylglucosamine (NAG), a naturally amino sugar.

CombiMAX contains sodium hyaluronate derived from bacterial fermentation of a Streptococcus strain, chondroitin sodium sulfate sourced from bovine cartilage, and NAG sourced from chitin, a naturally long-chain polymer of N-acetylglucosamine.

CombiMAX is a sterile viscoelastic solution processed by aseptic technique and supplied in a disposable glass syringe delivering 2.25 mLof solution.

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COMPOSITION:
Each pre-filled syringe contains sodium hyaluronate 36 mg, chondroitin sodium sulfate 67.5 mg, N-acetylglucosamine 67.5 mg, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium phosphate dodecahydrate, sodium hydroxide and/or hydrochloric acid (for pH adjustment), and water for injections.

INDICATIONS:
CombiMAX is indicated as a viscoelastic supplement or a replacement for synovial fluid in human knee joint. CombiMAX is indicated for symptomatic treatment of knee osteoarthritis. The actions of CombiMAX are lubrication and mechanical support.

CONTRAINDICATIONS:
CombiMAX is contraindicated in patients with:
- known allergy (hypersensitivity) to sodium hyaluronate, chondroitin sulfate, N-acetylglucosamine or to any components of CombiMAX
- pre-existing infections or skin diseases in the area of the intended injection site
- known infection of the index joint
- known systemic bleeding disorders, bleeding or tendency to bleeding

CombiMAX may contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of such allergies.

CombiMAX should not be used in patients with known allergy to derived bovine material.

CombiMAX should not be used in patients with known allergy to material derived from shrimps, crabs or seafoods.

WARNINGS AND PRECAUTIONS:
Although sodium hyaluronate, chondroitin sodium sulfate and N-Acetylglucosamine are biological components, the physician should be aware of the potential allergic risks inherent in the use of any biological material.

General precautions should be observed for the intra-articular injection administration. CombiMAX should be administered in the synovial knee joint space only by medical professionals trained in intra-articular administration technique.

An excess amount of CombiMAX is not to be used and the patient should be monitored closely. The intra-articular space should not be overfilled. If pain increases during the injection procedure, the injection should be stopped and the needle withdrawn.
Patients should be carefully examined prior to administration to determine signs of acute inflammation, and the physician should evaluate whether CombiMAX treatment should be initiated in this case.

Patients experiencing abnormal sequelae after intra-articular administration of CombiMAX should consult with a physician immediately.

The safety and effectiveness of CombiMAX have not been established in children and adolescents, pregnant or lactating women.

As no clinical evidence is available on the use of sodium hyaluronate and chondroitin sodium sulfate in patients with concomitant inflammatory arthropathy (such as rheumatoid arthritis, gouty arthritis), recent orthopedic surgery or trauma at the index joint, the treatment with CombiMAX is not recommended in these patients.

There were few case reports of increased INR (International Normalised Ratio) in patients receiving concomitant warfarin and glucosamine - chondroitin supplements. Due to limited information, caution is advised regarding the CombiMAX administration in patients taking anticoagulants or antiplatelet agents.

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Exacerbation of asthma symptoms after initiation of glucosamine supplements have been described (symptoms resolved after withdrawal of glucosamine), therefore, asthmatic patients should be aware of potential worsening of symptoms.

Verify the expiry date and the integrity of the packaging before use. Do not use CombiMAX after the "Use by date" shown on the packaging.
Do not use the syringe if its seal is opened or damaged.
The product is administered only if the solution is clear.
After opening, the contents of the syringe should be used immediately.
The product CombiMAX is for single use! Do not re-use. Each pre-filled syringe of CombiMAX is intended to be used once only for a single patient. The used needle and syringe must be discarded after injection and should not be kept for other administrations. Re-use of needles or syringes already used can lead to the transmission of infectious agents (including HIV and hepatitis).
Do not resterilize, as this may damage or alter the product.

UNDESIRABLE SIDE EFFECTS:
Intra-articular injection of CombiMAX can cause local undesirable side effects. Local symptoms as transient pain in the joint, transient swelling, heat feeling and redness have occasionally been observed following intra-articular injection of hyaluronate preparations.

Such effects can be minimized by applying a cold pack on the joint or by using medication such as painkillers for 24 hours after the injection. They usually disappear in a short time.

Cases of acute inflammation characterized by joint pain, swelling, effusion and sometimes joint warmth and/or stiffness, have been reported following an intra-articular injection with hyaluronic acid. Analysis of synovial fluid reveals aseptic fluid with no crystals. This reaction often responds within a few days to treatment with Non Steroidal Anti Inflammatory Drugs (NSAIDS), intraarticular steroids and/or arthrocentesis. Clinical benefit from the treatment may still be apparent after such reactions.

There are minimal risks associated with the procedure of injecting substances into joints in general, primarily infections and bleeding.

DOSAGE AND ADMINISTRATION:

CombiMAX must be administered strictly intra-articular. Do not inject the product extra-articularly.
Do not administer intravenously.

It is recommended to administer two treatment cycles per year, every 6 months, according to the doctor's recommendations.

Strict aseptic administration technique must be followed.
Injection site must be properly disinfected (70% alcohol or with another disinfectant). Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronic acid can precipitate in their presence.

Remove joint effusion, if present, before injecting CombiMAX. Arthrocentesis prior to injection is recommended.

Remove the pre-filled syringe from the package. Before administration, break the visible seal and remove the cap of the prefilled syringe. Attach to the syringe a sterile hypodermic needle with the appropriate size (gauge) and length (inch), and make sure you have it properly fixed by turning it slightly.
Common needle gauges for injections into the knee are 18 - 21 gauge (1 .2 - 0.8 mm). The final needle selection for any intra-articular procedure is determined by the physician.

Do not overfill the synovial space. It is the physician's responsibility to determine the appropriate volume and ensure that the joint is not overfilled.

Injection of subcutaneous lidocaine or similar anesthetic may be recommended prior to injection of CombiMAX.

As with any invasive joint procedure, it is recommended that the patient should avoid any strenuous activities or prolonged (i.e., more than an hour) weight-bearing activities such as jogging or tennis within the 48 hours that follow the intra-articular injection.

CHARACTERISTICS AND MODE OF ACTION:
CombiMAX is a product for viscosupplementation, which is a safe, effective and well established treatment in knee osteoarthritis consisting in injecting a hyaluronic acid based solution into the affected synovial joint. CombiMAX acts as a temporary replacement and supplement for synovial fluid.
CombiMAX relieves joint pain, improves articular mobility and protects cartilage.

Hyaluronic acid is a major component of the synovial fluid and cartilage and, thanks to its viscoelastic and rheological properties is responsible of the lubrication and cushioning in joints. It decreases friction between joint surfaces and protects soft tissue from trauma by acting as a shock absorber.

The quantity and quality of hyaluronic acid in the synovial fluid are reduced in the patients who have osteoarthritis because its synthesis by the synovial and cartilage cells is disturbed. The protection of articular surfaces thus is strongly altered, the cartilage becomes vulnerable and exposed to structural degradations due to the forces of friction and compression.

Chondroitin sulfate, a sulfate glycosaminoglycan, is an important structural component of the extracellular cartilage matrix. The role of chondroitin sulfate is to optimize the rheological behavior of hyaluronic acid, due to specific interactions.
Furthermore, in in vitro studies, chondroitin sulfate inhibits the main enzymes involved in destruction of the cartilaginous matrix: metalloproteinases and aggrecanases. Chondroitin sulfate also inhibits proinflammatory factors secretion. These data support the observed clinical activity as a symptomatic slow-acting for osteoarthritis with pain improvement and enhancement function.

N-acetylglucosamine significantly enhances the prevention of joint damage. Together with the chondroprotective effect of Hyaluronic acid, N-acetylglucosamine which has stimulatory effect on hyaluronic acid synthesis in human articular chondrocytes and synovial fibroblasts inhibits nitric oxide, cyclooxygenase-2 (COX-2), and IL-6 production, which in turn reduce apoptosis in cultured human chondrocytes. Chondroitin sulfate can also reduce apoptosis of chondrocytes via mitochondrial pathway.

CombiMAX, administered as a single injection, restores good lubrication and shock absorption in the knee joint, and it will provide significant improvement of symptoms.

Viscosupplementation with hyaluronic acid is an effective and well tolerated treatment for knee osteoarthritis. Viscosupplementation is a well tolerated treatment of other joints osteoarthritis but a consensus position at the world-wide level was not reached until now for the efficacy of viscosupplementation with hyaluronic acid for other joints osteoarthritis than knee osteoarthritis.

HOW SUPPLIED:
Each pre-filled syringe of CombiMAX contains 2.25 ml of a sterile viscoelastic solution of sodium hyaluronate 36 mg, chondroitin sodium sulfate 67.5 mg and N-acetylglucosamine 67.5 mg.
CombiMAX is available in carton box containing: one blister with a single-use prefilled syringe and Instructions for use.

CombiMAX is a medical device. To be used under the direction of a physician.

SHELF LIFE AND STORAGE:
Store at a temperature of 15 - 25°C, in the original package, in order to protect from light.
Do not freeze.

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ROMPHARM CO. **Manufacturer:/Proizvođač:**
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Authorized representative of the manufacturer in the Republic of Serbia:/Ovlašćeni predstavnik proizvođača u Republici Srbiji: VEMAX011 PHARMA DOO BEOGRAD - VOŽDOVAC, Mosorska 9, 11042 Beograd, Srbija **Number of the decision on the registration of the medical device:/Broj rešenja o registraciji medicinskog sredstva:** 515-02-01066-23-002 od: 09.06.2023.