EXPERT REPORT

Evaluation of Syalox 300 Plus in tablets for marketing authorization as a food supplement

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1. COMPOSITION OF THE PRODUCT

Composition Certificate

Product Name: Syalox 300 Plus (Triple Layer)
Pack Size: 20 tablets (~750 mg per tab)
Form: tablets
Shelf Life: 24 months

COMPONENTS	COMPOSITION (%)	PROPORTIONAL QUANTITY (mg)
Hyaluronic Acid Sodium Salt of which Hyaluronic Acid 240 mg per tab	39,87	300,00
Microcrystalline Cellulose	26,11	196,50
Boswellia Serrata ex. of which AKBA 10 mg per tab	13,29	100,00
Calcium Phosphates	12,36	93,00
Fatty Acids	4,65	35,00
Magnesium Salts of fatty acids	1,59	12,00
Silicon Dioxide	1,06	8,00
Sodium Crosslinked Carboxymethylcellulose	0,53	4,00
Colouring agent: E 132	0,20	1,50
Ethylcellulose	0,17	1,25
Polyvinylpyrrolidone	0,09	0,655
Hydroxypropyl Cellulose	0,05	0,40
Carnauba Wax	0,03	0,20
TOTAL	100	752,50

Orio Litta, 06/12/2016

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2. REGULATORY STATUS

Hyaluronic acid is a naturally occurring linear polysaccharide of the extracellular matrix of connective tissue, synovial fluid, and other tissues.

Hyaluronic Acid is a natural organic compound, synthesized by the Fibroblasts, composed by replicate sequences of Glucuronic Acid and NAcetilGlocosamine. After the age of 45 or because of traumas, the HA level in the tissues decrease in a progressive way, without the guarantee of the structural and protective functionality at the Cartilage of the joints, with the consequent inflammation and pain.

A 2008 American study, in which the Hyaluronic Acid was linked to a radioactive isotope (Technetium 99m) to permit the observation of its diffusion and concentration in the different organic districts, has demonstrated experimentally and unequivocally that the Hyaluronic Acid with high molecular weight, after the oral assumption, is really absorbed and spread in the joint connective tissue, included the Rachis.

Hyaluronic Acid is the active substance in many authorized supplement products indicated for the use in the treatment of the inflammatory process and is recognized and established in medical areas such as orthopedics, dermatology, and ophthalmology. Rheumatic diseases therapy, one of the most frequent causes of temporary and progressive invalidity of the modern age, provides especially structural, anti-inflammatory and analgesic activity treatments. Hyaluronic Acid (HA), of high molecular weight, associated with suitable anti-inflammatory substances like AKBA (Acetyl Keto Boswellic Acid), are efficient options for these types of diseases.

In general, Hyaluronic Acid and other ingredients are permitted for use in food supplements in EU member states.

Ask a doctor, pharmacist, herbalist, or other healthcare provider if it is safe to use this product if have:

liver disease
kidney disease
diabetes
low blood sugar (hypoglycemia)
thyroid disorder
free radicals activity
needs for antioxidants
immunomolulatory activity

Hyaluronic acid is likely safe when taken by mouth (orally) and when applied proparly and according the intake recommendations. Rarely, hyaluronic acid may cause allergic reactions

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3. HYALURONIC ACID

3.1 Kinetics

3.1.1 Hyaluronic Acid

A 2008 American study, in which the Hyaluronic Acid was linked to a radioactive isotope (Technetium 99m) to permit the observation of its diffusion and concentration in the different organic districts, has demonstrated experimentally and unequivocally that the Hyaluronic Acid with high molecular weight, after the oral assumption, is really absorbed and spread in the joint connective tissue, included the Rachis.

- After 15 minutes, significant concentrations of Hyaluronic Acid are observed in the blood and in the muscles.
- After 4 hours, significant concentrations of Hyaluronic Acid are observed in the joints of the shoulders and of the rachis.
- After 24 hours, significant concentrations of Hyaluronic Acid are observed in the joint connective tissue.
- The existence of Hyaluronic Acid is observed also 48 hours after the oral assumption (pic.2 – Diffusion and concentration of HA marked in the different organic districts).

The Inflammatory Processes characterized by various symptoms, like the loss of the involved tissue functionality, edemas formations, swelling and pain, are linked to the presence of the Leukotrienes. The Leukotrienes, formed in the metabolic pathway of the Arachidonic Acid for the intervention of a particular endogenous enzyme, belong to a group of mediators of the inflammation with chemotactic activity. They capture the immune cells (Polymorph nuclear Leukocytes) which locally operate releasing Elastase, proteolytic enzyme responsible for the destruction of the Collagen and of the tissues involved in the inflammatory process.

Pharmacokinetic studies have shown that HA is distributed rapidly in the synovial membrane. The highest concentrations of HA are found in the synovial fluid and the joint capsule, followed, in decreasing order, by the synovial membrane, the ligaments and the adjacent muscle.

Studies in animals have shown that breakdown takes place in the tissues surrounding the joints, although the principal route of metabolism is the liver. HA is eliminated from the synovial fluid in 2 or 3 days and is excreted mainly via the kidneys.

3.1.2 Acetyl Keto-Boswelic Acid

The anti-inflammatory activity of the **3-O-Acetil-11-Keto-Beta-Boswelic acid (AKBA)**, *Boswellia serrata* active component, is expressed primarly trough the selective inhibition, non competitive and reversible, of the 5-Lipoxygenase (5-LO), with the consequent block of the Leukotrienes synthesis. The use of Boswellia, with high **3-O-Acetil-11-Keto-Beta-Boswelic acid (AKBA)** concentrations in the inflammatory diseases, does not produce the gastrodamaging side effects, typical of the non-steroidal anti-inflammatory drugs (NSAID), because it doesn't operate on the synthesis of the prostaglandin catalyzed by the Cyclooxygenase enzyme.

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In fact is known that the use of NSAID can cause problems in the Glycosaminoglycan synthesis (GAG), accelerating the damaging process of the joints interested by the arthrosis diseases. The **AKBA, Acetil-11-Keto-Beta-Boswelic acid**, is a powerful inhibitor of the mediators of the inflammation and the natural pain:

- It inhibits the action of the 5-Lipo-Oxygenase enzyme (5-LO), implicated in the biosynthesis of the Leukotrienes, mediators of the inflammation. The result is the reduction of the joints swelling and the morning stiffness and it helps to improve the joints mobility;

- It destroys the activity of some Matrix Metalloproteases, in particular the activity of MMP-3, protecting the cartilages from the collagen decomposition;

- It prevents the induction of the expression of MMP from the necrotizing alpha factor (TNF-alpha), a dangerous pro-inflammatory cytokine, which level frequently increase in the ancient people ;

- In the Cartilages and in the joints tissues the AKBA, inhibiting the production of MMP, which destroys selectively the peptide bonds and the structure proteins, it prevents the removal of the Collagen, protecting the Cartilage and the joints liquids from the decomposition;

- The AKBA shows the optimal absorbing, fast action times, excellent tolerance, demonstrated with the confirmation that the use, also for a long time, does not cause secondary effects at a digestive effect, preserving the gastric mucosa from the ulcers. Its use generates a consistent improvement of the pain parameters and a significant sensation of relief and joint mobility that can persist for a long time.

3.2 Toxicity

Toxicity, mutagenicity and reproductive-toxicity tests have been negative in all cases.

3.3 Drug interactions

It is currently not known whether hyaluronic acid interacts adversely with other medications. You should nevertheless inform your doctor before taking any medications while you are getting hyaluronic acid.

4. PHARMACOLOGY

Hyaluronic acid

Endogenous synthesis

Recommended intake: 300 mg Hyaluronic Acid daily

HA is available in four forms: liquid injectable, oral capsule, oral liquid and skin cream. Whether HA taken works or not is related to percentage of total supporting ingredients, molecular size and dosage. Oral dosage should be 150 mg per day, with possibly a loading dose for one month of 300 mg per day. More HA is not always better.

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HA in an injectable form ranges from 3 million to 6 million daltons molecular weight, while some oral forms are as low as about 1,500 to 3,000 daltons. A Dalton is a unit of mass equal to the mass of a single hydrogen atom. Smaller molecular weight forms of HA are more easily absorbed in the intestines.

4.1 Characteristics

Syalox 300 Plus is a formulation in three layers, developed with patented technology, that includes 300 mg of Hyaluronic acid obtained by biofermentative technology (2 Hyaluronic acids with 2 different molecular weight to improve the bioavailability: 150 mg of HA on every external layer) + 10 mg of Acetyl Keto Boswellic Acid (contained in 100 mg of Boswellia), in the middle layer.

4.2 Rational

Hyaluronic acid is a safe substance and it is experimentally proved that only the hyaluronic acid with high molecular weight:

Is well absorbed after oral administration and it spreads in the articular connective tissue with manifold functions:

- it regenerates the articular Collagene
- it stimulates the biosynthesis of hyaluronic acid
- it has antioxidant action
- Acetyl keto boswellic acid (AKBA) has a specific powerful anti-inflammatory effect on the articular tissue.

The Hyaluronic acid with high molecular weight, orally administered, is well absorbed by the organism and it spreads in the articular connective tissue.

4.3 General Functions in the body

Hyaluronic acid is present in every tissue of the body. The water-binding capacity is directly related to the molecular weight of the molecule. Up to six liters of water may be bound per gram of HA. While most of the focus about hyaluronic acid has been on its lubricating, spacer filler, aging and skin enhancements, more recent research credits HA with more important but less understood role of communication between cells.

The amount of HA in cells, dependent on molecular weight size, is linked to numerous complex functions:

- reduces nerve impulses and nerve sensitivity associated with pain
- has an anti-inflammatory effect.
- facilitates biochemical processes in many tissues and organs of the body, such as the brain, heart, liver, skin, synovial fluid in joints, cartilage, eyes and developing embryos.
- attaches to collagen and elastin to form cartilage.
- lubricates movable joints and muscles.
- increases supplies of joint-lubricating synovial fluid.
- acts as a shock absorber in joints.

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- signals for other cells within the body to respond. [Hyaluronan also acts as a signaling molecule by interacting with cell surface receptors and regulating cell proliferation, migration, and differentiation.]
- helps deliver nutrients to and carry toxins from cells that do not have a blood supply, such as those found in cartilage.
- encourages water retention in other bodily tissues.
- moisturizes and binds water to the skin.
- prevents tissue dehydration.
- fill fluid in space between cells.
- holds cells together.
- helps to heal the body.
- helps relieve pain.
- prevents scarring
- serves as a barrier against disease
- promotes a youthful appearance.
- enhance transport of drugs via HA-human growth hormone complex

4.4 Aging Skin

HA is used in skin care creams and lotions since it helps to moisturize the skin and combat the dryness and loss of elasticity that occurs in aging skin that has been depleted of youthful HA stores. The anti-inflammatory effects of HA also carry important implications for collagen regeneration in maintaining healthy skin.

4.5 Dry Eyes and Eye Discomfort

The fluid inside the eye socket (called the vitreous humor) is composed almost completely of hyaluronic acid. Hyaluronic acid can help relieve chronic dry eyes by replenishing moisture within the eye socket, helping with tear production and restoring fluid balance. Some studies have also found that hyaluronic acid helps suppress oxidative damage caused by UVB light within the cornea. Doctors commonly use lubricating HA formulas to treat eye injuries and disorders, including cataracts, especially at the time before or after surgery when the eyes are most sensitive and dry. HA can be beneficial during eye surgery or recoveries, including after cataract removal, corneal transplant or repair of a detached retina.

4.6 Wound Healing

Topical hyaluronic acid has been shown to accelerate wound healing - in part by protecting tissue from oxygen free-radical damage in a number of studies. Scientists have noted its beneficial effects both immediately after the injury occurs and in long-term wounds as well. HA treatment has been reported to cause a 70 percent reduction in the surface area of wounds. Studies also have documented HA's effectiveness in leg ulcers and pressure wounds (bed sores).

HA is naturally present in high concentrations in the skin and soft connective tissues. Therefore, HA is an appropriate choice for a matrix to support dermal regeneration and augmentation. For example, Prestwich and co-workers found that cross-linked HA hydrogel films accelerate the healing of full-thickness wounds, presumably by providing a highly hydrated and nonimmunogenic environment that is conducive to tissue repair.

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4.7 Oral Health

Researchers have successfully used topical HA gel to enhance periodontal health. In patients with chronic periodontitis who underwent periodontal surgery, HA gel improved gingival recession and the clinical outcome.

In another study of patients with periodontal disease, application of hyaluronan-containing gels after scaling and root planing resulted in a significantly reduced probing depth. Additionally, dentists who used hyaluronic acid in children with gingivitis, combined with the standard treatment, noted that HA markedly improved the treatment outcome.

4.8 Chondroprotective effects

HA has been experimentally studied as a potential agent of therapeutic intervention in osteoarthrosis (OA). Hyaluronid acid has been applied to the therapy of experimental OA. Investigations have shown that intra-articular injection of HA reduces arthritic lesions in experimental animal models of articular cartilage injury.

HA has been used in osteoarthritis for more than 30 years. Many studies have documented the long-lasting pain-relieving effects of intra-articular supplementation with HA in subjects with knee osteoarthritis, a procedure that was approved by the FDA in 1997. Oral supplementation with HA also shows promising results as showed in many studies. The impressive results seen with oral HA supplementation may be particularly advantageous in elderly subjects in whom osteoarthritis-related pain results in a serious limitation of activities of daily living. Oral supplementation also has obvious advantages over intra-articular HA by avoiding potential complications at the injection site and discomfort associated with repeated injections.

Clinical studies have confirmed anti-inflammatory, anabolic and cartilage-protective actions of HA in reducing pain and improving patient function. HA has a stimulatory effect on the metabolism of chondrocytes (cells found in the cartilage) through its interaction with CD44 receptors.Researchers have speculated this could lead to permanent improvement of cartilage with oral supplementation, which can elevate plasma HA concentrations over a long time period.

4.9 Orthopaedic applications

HA plays a vital role in the development of cartilage, the maintance of the sinovial fluid and the regeneration of tendons. High concentrations of HA have been found in the ECM of all adult joint tissues, including the sinovial fluid and the outer layer cartilage (Leach and Schmidt, 2004). In part because of its viscoelastic nature and ability to form highly hydrated matrices, HA acts in the joint as a lubricant and shock absorber. The pathologic changes of synovial fluid hyaluronic acid, with its decreased molecular weight and concentration, led to the concept of viscosupplementation.

A healthy knee contains about two ml of synovial liquid and the Hyaluronic Acid concentration in it is from 2.5 to 4 mg/ml (0.25 – 0.4%). The patients with osteoarthritis have a 2-3 times lower rate of synthesis and concentration of Hyaluronic Acid in synovial liquid compared to the normal rate, reduction of the molecular weight of Hyaluronic Acid due to accelerated hydrolysis, and reduction of viscoelastic properties. As a result, the friction of the surfaces of the cartilage increases as well as destruction of cartilage and bone tissue.

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4.10 Viscosupplementation

Viscosupplementation is a novel, safe, and possibly effective form of local treatment for osteoarthritis (Uthman et al., 2003). Viscosupplementation with HA products helps to improve the physiological environment in an osteoarthritic joint by supplementing the shock absorption and lubrication properties of osteoarthritic synovial fluid. The rationale for using viscosupplementation is to restore the protective viscoelasticity of synovial hyaluronan, decrease pain, and improve mobility. The immediate benefits of viscosupplementation are the relief of pain. Longerterm benefits are believed to include the return of joint mobility by the restoration of transsynovial flow and, ultimately, the metabolic and rheologic homeostasis of the joint (Wang et al., 2004). Viscosupplementation came into clinical use in Japan and Italy in 1987, in Canada in 1992, in Europe in 1995, and in the United States in 1997.

4.11 Antiadhesion applications

As HA is highly hydrophilic, it is a polymer that is well suited to applications requiring minimal cellular adhesion. Postoperative adhesions, which form between adjacent tissue layers following surgery, impede wound healing and often require additional surgical procedures to be repaired successfully. Barriers made from cross-linked HA have been effectively used to prevent such adhesions from forming. Furthermore, the adhesion of bacteria to biomaterials can induce infections and constitute a great risk to the patient; with this in mind, esterified HA has also been used to prevent bacterial adhesion to dental implants, intraocular lenses, and catheters (Leach and Schmidt, 2004).

4.12 Ophthalmology

HA, a natural component of the vitreous humor of the eye, has found many successful applications in ophthalmologic surgery. HA is particularly useful as a spacefilling matrix in the eye; thus, intraocular injection of HA during surgery is used to maintain the shape of the anterior chamber. Furthermore, HA solutions also serve as a viscosity-enhancing component of eye drops and as an adjuvant to eye tissue repair.

4.13 Cardiovascular applications

In a manner related to its antiadhesive properties, HA has also proven to be effective for increasing the blood compatibilities of cardiovascular implants such as vascular grafts and stents. For example, biomaterial surfaces treated with cross-linked HA have been associated with reduced platelet adhesion and thrombus formation (Leach and Schmidt, 2004). Furthermore, sulfated HA derivatives can act as heparin mimics (Barbucci et al., 1995); in fact, HA derivatives with higher degrees of sulfation are associated with increased abilities to prevent blood coagulation (as measured by longer times required for whole blood clotting) (Barbucci et al., 1995).

4.14 Hyaluronic Acid in Immunology

The immune system is directly connected with Hyaluronic Acid. Hyaluronan is included into drugs used for the complex treatment of immunodeficient conditions associated with viral diseases. At a molecular level, the mechanism of action of the biopolymer is connected with the blocking of several molecular inflammation factors. On one hand, Hyaluronic Acid activates inferonogenesis, but on the other hand, it increases action of the interferon inductor (for example, double-stranded RNA). Interferon is produced mainly by the activated monocytes and T-cells of the immune system. The interleukins-2 and -5 (IL-2, IK-5) play a major role in the activation of T-cells, which, in turn, activate synthesis of Hyaluronic Acid by endothelial capillary cells.

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Then Hyaluronic Acid stimulates synthesis of CD44 receptors, which is the key event for the activation of the lymphocytes and monocytes. Hyaluronic Acid is used alone or in combination with interferon to slow down the development of the infection by the virus herpes simplex by application on the infected epithelium. The obvious antimicrobial action of Hyaluronic Acid can be achieved by its crosslinking with hydrophilic polymers, which are capable for accelerated penetration through cell membranes or intercellular gaps.

5. CONCLUSION

The population is aging rapidly around the world. In addition to medical treatment, self-medication is more commonly practiced to reduce patient burden and enhance. HA is a safe raw material and the efficacy of oral HA in relieving knee pain was demonstrated in several clinical trials. HA as a dietary supplement exhibits mild efficacy and no side effects. By utilizing these characteristics, HA dietary supplements provide at least some possibility for the treatment and prevention of serious conditions in patients with OA exhibiting mild knee and joint pain. This review may improve the understanding of HA dietary supplements and it is expected that HA will emerge as a modality for treating knee pain that can be safely used by patients.

HA is a vital component of cellular structure and offers a multitude of benefits including anti-inflammatory and antioxidant effects, pain-relief, joint lubrication and cartilage-protection, collagen regeneration, and enhancement of cell viability. Since HA declines naturally with age, oral HA supplementation offers an efficient alternative, which is well absorbed through the highly vascularized oral mucosa that is rich in CD44 receptors. As a result, oral HA supplementation offers an effective solution for joint protection, maintaining healthy skin and eyes, and is a useful adjunct for good dental hygiene.

The ingredients included in this food supplement are all contained in the Annex II of Directive 2002/46/EC as amended by EC 1170/2009 and the amounts that are consumed daily based on the recommended dosage of 1 tablet / day are well under the established tolerable upper intake levels as stated in the EFSA document under the title “tolerable upper intake levels for vitamins and minerals”.

Approved

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