Synolis VA Product **Monograph**

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1 Abbreviations

AE	Adverse Event
SAE	Serious Adverse Event
BMI	Body Mass Index
CEP	Clinical Evaluation Plan
CI	Confidence interval
CIP	Clinical Investigation Plan
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
EUROVISCO	EUROpean VIScosupplementation COnsensus group
FDA	Food and Drug Administration
HA	Hyaluronic Acid
HMW	High molecular weight
IA	Intra-articular
IFU	Instructions For Use
ITT	Intention-To-Treat
KOOS	Knee injury and Osteoarthritis Outcome Score
LMW	Low molecular weight
MCII	Minimal clinically important improvement
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive
MDR	Medical Device Regulation
MEDDEV	MEDical DEVice (i.e. European Commission's official guidance for medical devices)
MID	Minimum important difference
MMW	Medium molecular weight
MW	Molecular weight
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT-OARSI	Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International
PMCF	Post-Market Clinical Follow-up

2 Executive summary

SYNOLIS VA 40/80 and SYNOLIS VA 80/160 (hereinafter referred to as SYNOLIS VA), manufactured by Aptissen SA are classified as a Class III medical devices according to Rule 8 of Annex VIII of the European Medical Device Regulation (MDR) 2017/745.

SYNOLIS VA 40/80 has been CE-marked and marketed in Europe since 2009 under the MDD 93/42/EEC, as amended by the directive 2007/47/EC. The CE mark was obtained by Aptissen in 2014. SYNOLIS VA 40/80 is also distributed under the brand name GO-ON® Matrix and HYLASTO S. SYNOLIS VA 80/160 has been CE-marked since 2019.

Performance of SYNOLIS VA in the treatment of symptomatic OA is achieved through high concentration and high mean molecular weight of sodium hyaluronate combined with sorbitol. This unique combination confers to this gel its ability to restore joint lubrication and its shock absorbing properties similar to those of the healthy synovial fluid.

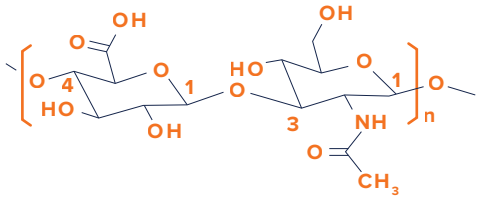
SYNOLIS VA reduces local pain and discomfort caused by symptomatic OA and improves mobility of the synovial joints of the knee and hip (for hip, SYNOLIS VA 80/160 only).

Clinical safety, performance and benefits of SYNOLIS VA when used as treatment of symptomatic OA, in order to reduce pain and improve mobility in its target treated population, were demonstrated and supported by broad clinical evidence. In patients with knee osteoarthritis (OA): A total of 3 studies (n=643 patients) supported the use of a single injection of SYNOLIS VA 40/80; 5 studies (n=325 patients) supported the use of a single injection of SYNOLIS VA 80/160, and 2 studies (n=455 patients) supported the use of 3 weekly injections of SYNOLIS VA 40/80.

In patients with hip OA: A total of 2 studies (n=57 patients) supported the use of a single injection of SYNOLIS VA 80/160.

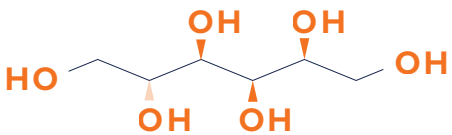
The **benefit/risk** ratio was considered as acceptable for SYNOLIS VA when used in accordance with its intended purpose in its target treated population, as long as intended users are appropriately informed about known limitations and risks associated with the use of such device.

Hyaluronic acid



D-gluouronic acid N-acetyl-glucosamine

Sorbitol



› The structure of **hyaluronic acid** https://www.glycoforum.gr.jp/article/01A2.html and of **Sorbitol** https://www.medchemexpress.com/d-sorbitol.html

3 Introduction to osteoarthritis and viscosupplementation of the knee

Normal knee joint

The knee joins the femur, patella and tibia and their cartilage with a fibrous joint capsule. The joint capsule is continuous with the periosteum of the joined bones and constitutes the outer boundary of a synovial cavity. It surrounds the bones' articulating surfaces. The structure and function of the anatomical parts are presented in Table 1.

Table 1. The anatomical parts and function of the knee

Anatomical parts	Structure	Function
Synovial cavity	Characteristic space between the bones, filled with synovial fluid	Allows movement in joint
Joint capsule	Fibrous capsule, continuous with the periosteum of articulating bones, consists of two layers (the outer fibrous membrane and the inner synovial membrane), highly innervated	› Outer fibrous membrane: isolation and mechanical by ligaments › Inner synovial membrane: production of synovial fluid
Cartilage	Lines the epiphyses of joint end of bone with a smooth surface	Functions to absorb shock and reduce friction during movement
Menisci	Fibrocartilage pads between opposing surfaces	Fill space and improves stability of the joint
Fat pad	Adipose tissue pad	Protects the articular cartilage
Tendons	Dense regular connective tissue cords	Improves stability of the joint
Accessory ligaments	Fibres of some fibrous membranes arranged in parallel bundles of dense regular connective tissue	Resist strains to prevent extreme movements that may damage the articulation

The synovial fluid is clear and viscoelastic fluid that fills all cavities within knee joint. Its viscoelasticity is a time-dependent elastic behaviour. It functions as natural lubricant that protects the intraarticular surfaces, including the cartilage from both damage and wear during motion. In humans, hyaluronic acid is present as sodium hyaluronate. Sodium hyaluronate together with a large mucinous protein called lubricin (also known as proteoglycan-4) provide viscosity and a low-friction state. The articular cartilage provides smooth, low-friction surface that allows for the normal gliding motion of the joint. It also contains hyaluronic acid. The protection of the cartilage is very important, as the knee achieves movement on small contacting surfaces, which bear high pressure.

Osteoarthritis of the knee

Osteoarthritis of the knee is a chronic arthropathy and one of the most common causes of chronic disability in adults. Osteoarthritis is classified as primary (idiopathic) or secondary to some known causes (conditions that change the microenvironment of the cartilage, including significant trauma, congenital joint abnormalities and metabolic defects).

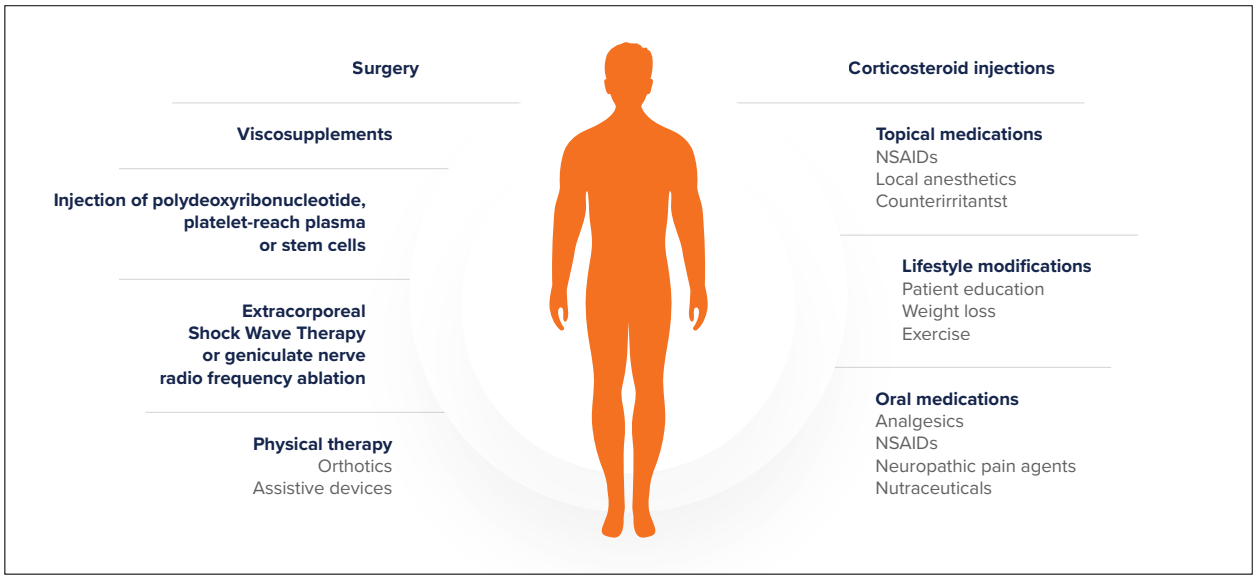
Pathologically, osteoarthritis represents failed repair of joint damage resulting from mechanical stresses. Osteoarthritis is a disease of the whole joint. It is characterized by disruption and potential loss of joint cartilage along with other joint changes, including bone hypertrophy (osteophyte formation) and the inflammation of the synovia. Its progression varies among persons and within a knee over time. Symptom severity and structural damage on imaging are often discordant. The symptoms include gradually developing pain aggravated or triggered by activity, stiffness lasting <30 minutes on awakening and after inactivity and occasional joint swelling. Episodic pain is predictable in early stages but becomes less predictable and more distressing in late stage. Typically, knee pain limits activity and impairs quality of life. The risk of immobility is significant. Plain radiographs underestimate the joint tissue involvement in osteoarthritis, since they visualize only cartilage loss (joint space narrowing) and bony changes (subchondral sclerosis, cysts, osteophyte formation). Once these are apparent on radiographs, the condition has significantly advanced. Magnetic resonance imaging studies can detect early disease and have provided evidence of matrix changes in cartilage, synovitis, bone marrow lesions and degenerative changes in soft-tissue structures beyond the cartilage, including ligaments and the knee menisci.

Treatment, including viscosupplementation

The treatment approach may be stepwise or multimodal. [1]

The multimodal approach is presented on *Figure 1*. The foundation of both treatment approaches is patient education about the value of lifestyle modifications for improving joint pain. These measures can improve patient confidence in movement and exercise. Lifestyle changes may be easier to achieve, if pain is not a barrier. Surgical intervention with total knee arthroplasty is late and costly step, that may result in additional morbidity.

Figure 1. Multimodal osteoarthritis therapy [2]



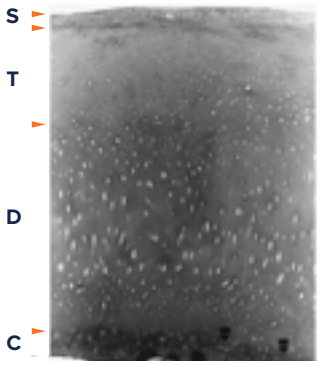
NSAID: nonsteroidal anti-inflammatory drug

The therapeutic goal of administration of intraarticular sodium hyaluronate is to provide and maintain intraarticular lubrication, which increases the viscoelastic properties of synovial fluid. This form of therapy is therefore termed “viscosupplementation.” It is also suggested, that hyaluronate exerts secondary effects, like antiinflammatory, analgesic and possibly chondroprotective actions on the articular cartilage and joint synovium. The clinical benefits of treatment with intraarticular hyaluronate, which may persist well beyond the intraarticular residence time of the product, have been suggested to be caused by the reestablishment of joint homeostasis as a result of an increase in the endogenous production of hyaluronate. As other local therapeutic interventions, viscosupplementation is also a particularly attractive approach for OA treatment because it can diminish some of the severe side effects associated with systemic delivery, mainly in the elderly.

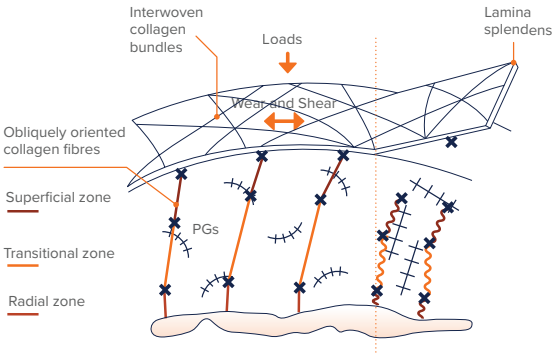
4 Cartilage, synovial fluid, synovial membrane in health and osteoarthritis

The articular cartilage consists of four horizontal layers: the superficial, transitional, deep and calcified cartilage zones. (*Figure 2. A*) The zonal organization is of functional importance. Cells in various layers differ in size, shape, and metabolic activity. In adult humans, cell density is highest at the articular surface and decreases with increasing distance from the surface, as well as with advancing age in every zone of the tissue.

Figure 2. Structure of the articular cartilage



A Articular cartilage with signs of mild degeneration from the medial femoral condyle of a 60-year-old female patient who received a total knee endoprosthesis because of advanced gonarthrosis. Four zones of cartilage are clearly visible: (S) superficial with lamina spledens, (T) transitional, (D) deep, and (C) calcified zone. [3]

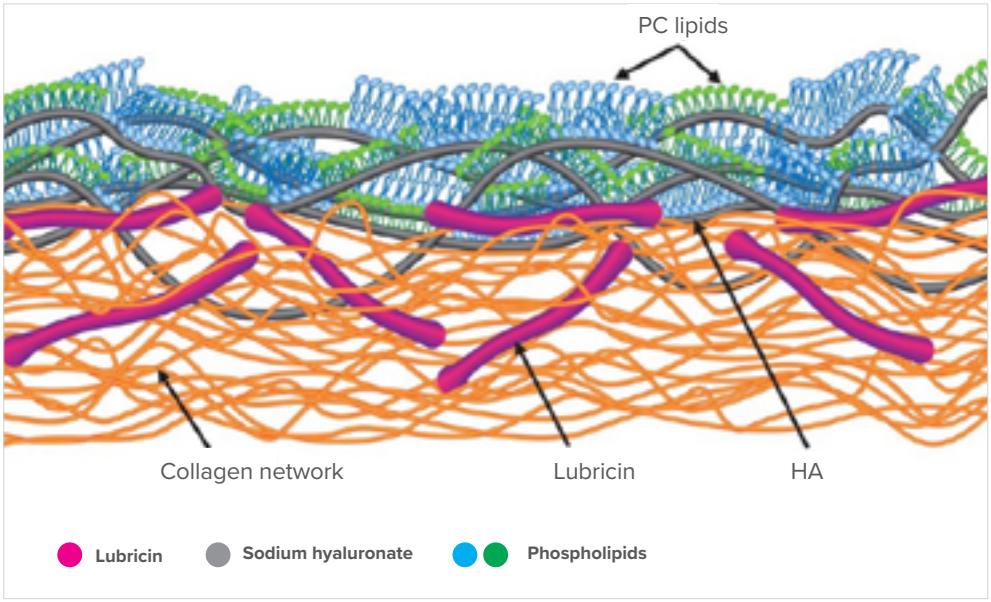


B A schematic structure of the collagen network in articular cartilage shows that the interwoven collagen bundles in the lamina splendens integrate the obliquely oriented collagen fibres and those in the deeper region to form a 3D collagen scaffold, which anchors to the subchondral bone. It reinforces the swelling pressure of proteoglycan gel to provide the articular cartilage with loading capacities and considerable tensile strength to withstand for wear and shear stresses. [4]

Hydration lubrication is the current theory for understanding the friction and lubrication on the articular surfaces. Lubricin is present in synovial fluid and on the surface of articular cartilage. Lubricin is a large glycoprotein that consists of approximately equal proportions of protein and oligosaccharides. It traps large quantities of water and is stabilised by a fluid-like cushioning layer, which enables bottle brush polymers to lower the friction between joints when external pressure is applied.

Interfacial fluid film formed from the synovial fluid takes place in the lubrication during physical activities. Lubricin molecules known to reside in the outer superficial zone of cartilage and to be attached to its surface, interact with and immobilize sodium hyaluronate molecules at the surface. Together, the hyaluronic acid and lubricin molecules form a complex with phospholipids whose outer exposed and highly hydrated phosphocholine head groups reduce friction via the above described hydration lubrication mechanism. (*Figure 3.*)

Figure 3. Structure of the boundary layer at the articular surface [5]



Because of their large electric dipoles, water molecules form hydration shells around the polar groups of the phospholipids, lubricin and hyaluronic acid. Large energy is required to break up these shells. The individual water molecules in each shell can exchange positions with surrounding bulk water or with water in adjacent shells. [5]

Long-term standing is a static loading position all synovial fluid forming the film flow out from between the load-bearing articular surfaces. (boundary lubrication) The only barrier against direct solid-to-solid contact of the articular surfaces is the adsorbed molecular film on the surface of lamina splendens, the superficial zone on *Figures 2, 4.*

During usual physical activities the bearing surfaces of the knee are close to each other, but still separated by a highly pressurized fluid film, that causes elastic deformation of the articular surfaces (elasto-hydrodynamic lubrication).[6] The pressure and thickness of the hydrodynamic film depend on both the rheological properties of the synovial fluid and the elastic deformation of the bearing surfaces.

During high speed movements (hydrodynamic lubrication) [6] there is a thick interfacial fluid film between the articular surface, because when two surfaces slide past each other a wedge/entraining flow of the synovial fluid is generated. The narrowing wedge-shaped gap produces a hydrodynamic pressure in the fluid, that tends to push the two surfaces apart.

The thickness of the film made by the synovial fluid is much larger than the heights of the tallest asperities. The normal load is transmitted through the pressurized fluid film. During mixed lubrication both the elastohydrodynamic and boundary lubrication conditions have role. Fluid pressurization may move in or move out some fluid into the cartilage surface. Hyaluronic acid has important role in all these cartilage lubrication mechanisms.

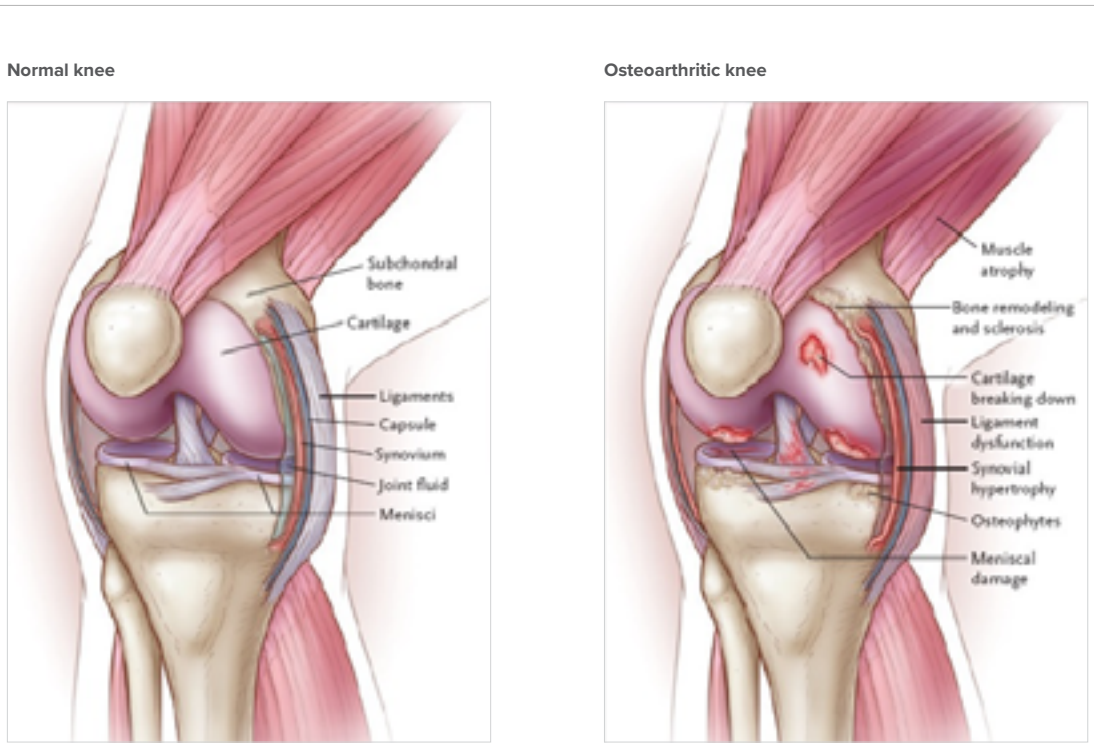
In osteoarthritis there is a progressive deterioration of the knee's articular cartilage, synovia and synovial fluid's anatomy and function.

It is generally divided into three broad stages [7]:

- **Stage I:** proteolytic breakdown of cartilage matrix.
- **Stage II:** fibrillation and erosion of cartilage surface, which is accompanied by the release of breakdown products into the synovial fluid.
- **Stage III:** synovial inflammation begins when synovial cells produce proteases and proinflammatory cytokines.

Figure 4. presents the macroscopic changes in the osteoarthritic knee. Bone sclerosis occurs due to the increased production of collagen that is improperly mineralized. Osteophytes form at the joint margins, often at the insertion site of tendons or ligaments. In more advanced disease, bone cysts occur. Soft-tissue components of the joint, including ligaments, the joint capsule, and the menisci commonly exhibit disruption of their extracellular matrix and loss of cells. Periarticular muscles and nerves are also affected.

Figure 4. Comparison of normal and osteoarthritic knee [8]



Differences between the normal and osteoarthritic knee with regards to the involvement of articular and periarticular tissues.

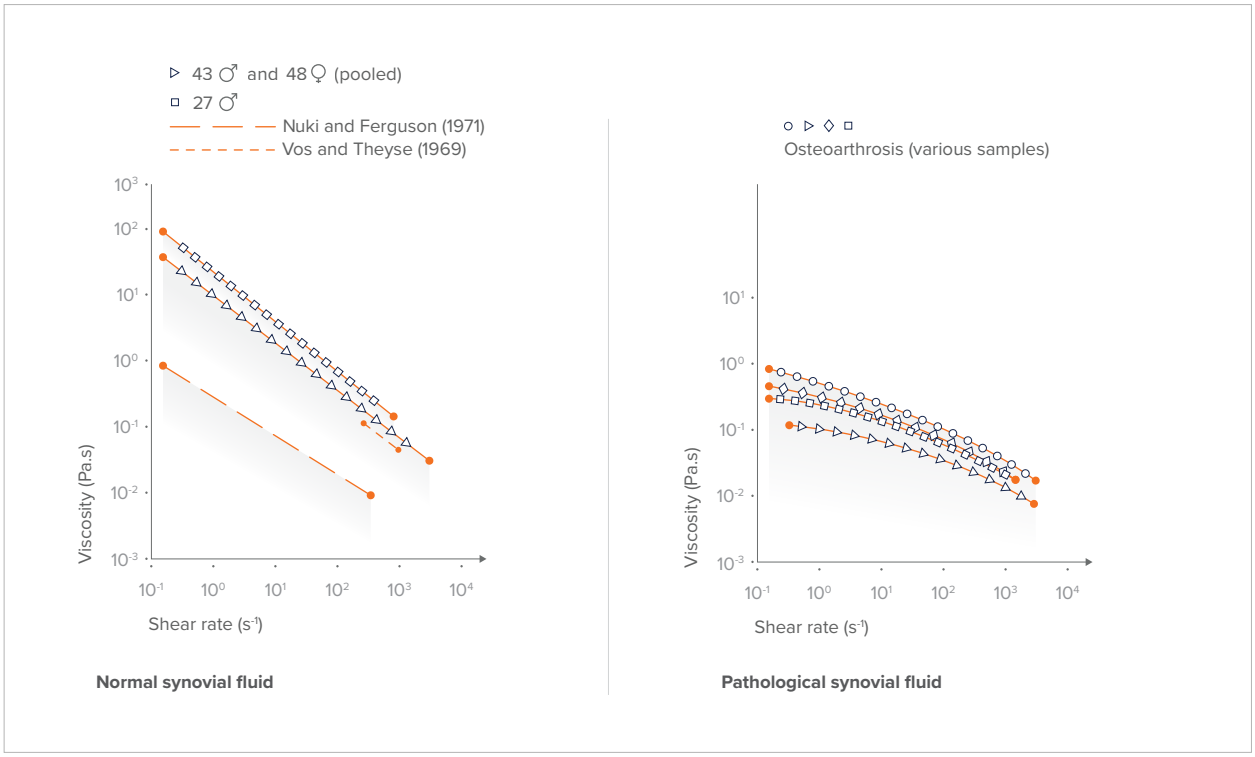
Sodium hyaluronate is responsible for the rheologic properties of synovial fluid. The composition of the synovial fluid changes in osteoarthritis. (*Table 2.*) In osteoarthritis, synovial hyaluronate is partially depolymerized, which leads to reduction of the molecular mass and the viscoelasticity of the synovial fluid. [9]

Table 2. Composition of normal and osteoarthritis synovial fluid [9]

Components	Normal	Osteoarthritis
HA MW (MDa)	6.3-7.6	1.6-3.48
HA (mg/ml)	2.5-3.65	1.07-2.6
Protein (mg/ml)	10.4-15.8	17.0-56.8
Phospholipids (mg/ml)	0.13-0.15	0.26-0.98
Total cholesterol (mg/ml)	0.07-0.08	0.04-1.69
Triglycerides	0	0.12-0.59
HA=hyaluronic acid, MW=molecular weight, MDa=Dalton 106		

Figure 5 [10] presents the viscosity ranges of human synovial fluid at health and disease. Normal synovial fluids and pathological ones can be readily differentiated by means of their rheological properties. The viscosity at low shear rates is significantly reduced in osteoarthritis. The synovial fluid of diseased joints suffers a decrease in viscosity at all shear rates.

Figure 5. Viscosity of the synovial fluid in healthy and osteoarthritic joints

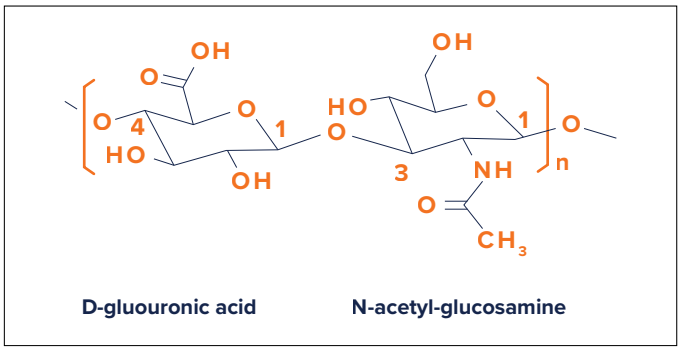


5 Physicochemical properties of sodium hyaluronate and sorbitol

Sodium hyaluronate is hygroscopic, water-soluble glycosaminoglycan. It has many pharmaceutical, medical device and cosmetic applications. [11]

It is composed of disaccharides of alternating D-glucuronic acid and N-acetyl-D-glucosamine linked by ß-(1➔3) and ß-(1➔4) glycosidic bonds, respectively. (*Figure 6.*) The molecular weight of each disaccharide is 401 Daltons (Da). The number of repeat disaccharides in a completed linear hyaluronate molecule can reach 10,000 or more. The average length of a disaccharide is ~1 nm. Thus, a molecule of 10,000 repeats could extend 10 µm.

Figure 6. The structure of hyaluronic acid [12]

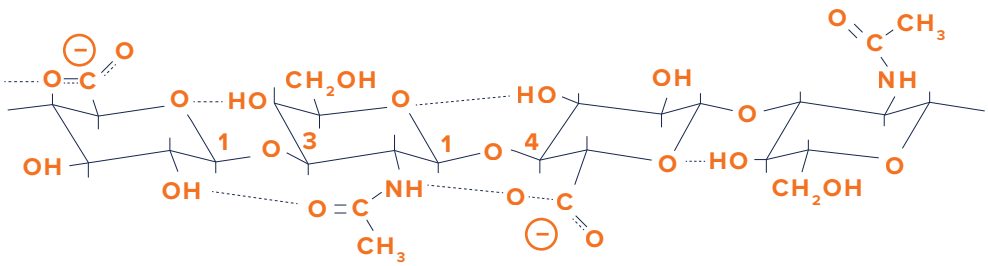


Alternating D-glucuronic acid and N-acetyl-D-glucosamine linked by ß-(1➔3) and ß-(1➔4) glycosidic bonds

Electron micrograph of sodium hyaluronate molecules

Sodium hyaluronate is unbranched, negatively-charged and contains polar and apolar segments. In aqueous solutions sodium hyaluronate takes up a loosely coiled wormlike configuration that may be stabilized by dynamically forming and breaking intramolecular hydrogen bonds parallel to the chain axis (*Figure 7.*)

Figure 7. The schematic representation of hydrogen bond formation [13]



The potential hydrogen bonds may form both within the macromolecule and between adjacent molecules.

This configuration, combined with its high molecular weight and numerous mutually-repelling anionic groups, allows sodium hyaluronate to form a loosely entangled three-dimensional network. This structure ensures, that sodium hyaluronate is highly viscoelastic due to mutual macromolecular crowding effects. To ensure biocompatibility and good tolerability, the pH and the osmolality of marketed sodium hyaluronate gels are set to physiological range. The molecular weight and the concentration of sodium hyaluronate applied in medical devices have significant influence on the physicochemical properties and the characteristics of the product. As they increase the gel gets stiffer, due to the increasing number of hydrogen bond formations in the tri-dimensional molecular network. Water molecules fill up the space within the gel.

For clinical use viscosity, cohesivity and swelling factor might have importance as they are closely associated with the following characteristics: extrusion force required at application, speed of dispersion in the joint cavity and volume in the joint cavity at fluid equilibrium after injection, respectively. [14]

Sorbitol is humectant, water soluble polyhydric sugar alcohol, it occurs in nature in many plants including apples, pears, peaches, and prunes. It has many pharmaceutical, food and cosmetic applications and it is metabolised mainly in the liver to fructose. [15] It is used to keep the viscosity of hyaluronic acid based medical devices. [16]

6 Sources of hyaluronic acid and sorbitol

The sources of hyaluronic acid used in the medical devices are either animal tissues (usually rooster comb) or biosynthesis by genetically modified Bacillus. Recombinant production has also emerged as an attractive alternative. [17]

The molecular weight of hyaluronic acid depends on the source. Hyaluronic acid from animal materials has high molecular weight (up to 20,000 kDa). By contrast, bacterial hyaluronic acid has a molecular weight between 1000 and 4000 kDa; however, the enzymatic technique makes it possible to obtain polysaccharides with a range of molecular weight between 550 kDa and 2500 kDa. [18]

The molecular weight of sodium hyaluronate, as provided in the applicable documents usually stands for average molecular weight. The current evidence supports clinically important and significant treatment effects of intraarticular hyaluronic acid formulations with molecular weight over 1500 kDa. [19]

The molecular weight of the viscosupplements marketed in Europe it is in the range of 600-6000 kDa. [20] The molecular weight distribution of sodium hyaluronate containing products is important to consider, as short oligosaccharides may be included if the molecular weight distribution is wide and around a low average molecular weight. [21]

7 Current overview of efficacy and safety of IA injections of sodium hyaluronate for osteoarthritis

The intraarticular administration of medicinal products, medical devices or drug-medical device combinations is a particularly attractive approach for osteoarthritis treatment because the therapeutic agent may be delivered directly to the diseased area in high concentration and some of the severe side effects associated with systemic delivery can be diminished. There is a broad range of intraarticular treatment options for osteoarthritis, which are usually applied when persistent joint pain and significantly impaired knee function together lead to limited mobility. [22]

No complete list of viscosupplements marketed in the EU. Sodium hyaluronate and its derivatives are in use for the treatment of patients with knee osteoarthritis. They contain non-crosslinked and/or cross-linked sodium hyaluronate. The usual dose of sodium hyaluronate of the marketed medical devices is 40-80 mg/intervention. The injected volume is 1-4 ml. [23]

7.1. Efficacy

In a current literature search of the PubMed database in September 2021, 102 publications have been found with the search terms “hyaluronate, intraarticular injection” and the limit “humans”. Only meta-analyses and systematic reviews, that were published since September 2016 were reviewed. Systematic reviews and meta-analyses of randomized controlled trials and high-quality, single, randomized controlled trials are considered to be the highest quality/the strongest evidence. [24]

7.1.1 Molecular weight of sodium hyaluronate and its importance in viscosupplementation

The molecular weight of sodium hyaluronate, as provided in the applicable documents usually stands for average molecular weight. The current evidence supports clinically important and significant treatment effects of intraarticular hyaluronic acid formulations with molecular weight over 1500 kDa. [25]

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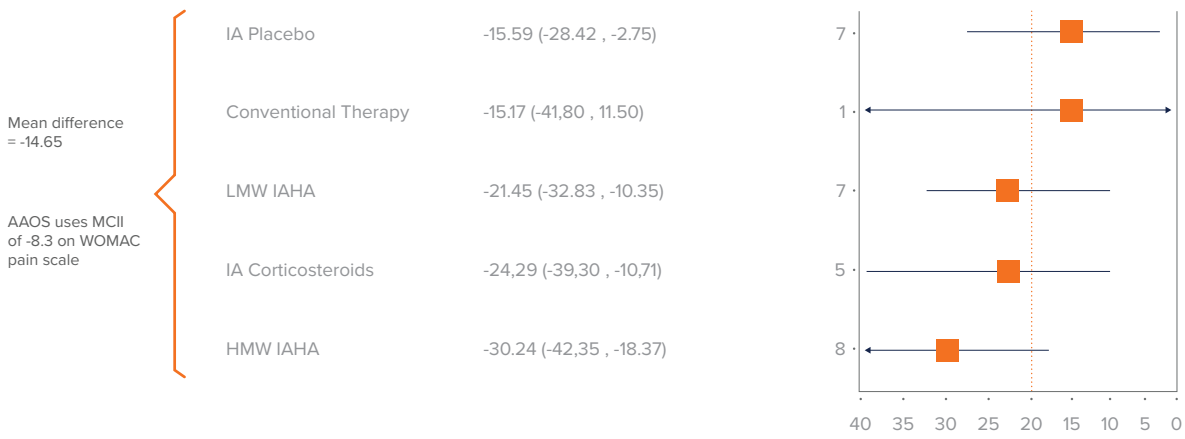
The results of a large network meta-analysis by Hummer et al. are presented in the *Figure 9.*

Figure 8. Absolute efficacy of intraarticular treatments and conventional therapy on WOMAC pain 0–100 scale [27]



SMDs were multiplied by median SD (25.8) to convert effect estimates back to WOMAC Pain Scale (0–100). AAOS = American Academy of Orthopaedic Surgeons; HMW = high molecular weight; IA = intraarticular; IAHA =intraarticular hyaluronic acid; LMW = low molecular weight; MCII = minimal clinically important improvement; SMD = standardized mean difference; WOMAC = Western Ontario and McMaster Universities Arthritis Index

Another network meta-analysis was published in 2020 as well. [28]

The study evaluated the efficacy and safety of intra-articular treatments of primary knee osteoarthritis in the short term (3 months follow-up), using a network meta-analysis design, while taking within-class differentiating factors into consideration. The treatments assessed were high molecular weight (≥ 3000 kDa) and low molecular weight (< 3000 kDa), hyaluronic acid injections, extended-release corticosteroids, standard-release corticosteroids, platelet-rich plasma (PRP), and saline. High molecular weight sodium hyaluronate was the only treatment to surpass the minimum important difference (MID) for both pain and function outcomes.

In a systematic review the minimum clinically important difference was developed to ascertain the smallest change in an outcome that patients perceive as beneficial. [29]

The objectives of the review were to compare :

- The minimum clinically important difference (MCID) for pain assessments used among guidelines and meta-analyses investigating different nonsurgical therapies for knee osteoarthritis and (2)
- The effect estimates of different nonsurgical interventions against a single commonly-utilized MCID threshold.

The analysis demonstrated that intra-articular hyaluronic acid, together with intra-articular corticosteroids, and acetaminophen all had relatively larger effect sizes than topical nonsteroidal anti-inflammatory drugs (NSAIDs). Higher-molecular-weight intra-articular hyaluronic acid had a greater relative effect compared with both non-selective and cyclooxygenase-2-selective oral NSAIDs.

A systematic review published in 2019 evaluated the anti-inflammatory effects of hyaluronic acid, that may be an additional effects to viscosupplementation. [30]

According to a systematic review published in 2018, the strongest evidence supported the clinically important and significant treatment effects of intra-articular hyaluronic acid formulations over 1,500 kDa. [31]

7.1.2 Delay in knee replacement surgery

The results of a study, published in 2020 provided a real-world understanding of the direct knee osteoarthritis–related costs. In patients who received hyaluronic acid injections and had knee arthroplasty during the study period, hyaluronic acid treatment resulted in only 1.8% of their overall knee OA–related treatment costs with a delay for surgical intervention by 15 months. (*Figure 13.*) [32]

In a retrospective and observational study in France, the time to total knee replacement was compared in patient who received at least one intraarticular sodium hyaluronate injection during their follow-up period, against those who received only intraarticular corticosteroid injections. The findings suggested that use of sodium hyaluronate was associated with a significant delay in total knee replacement. Approximately 7.5 years after diagnosis, patients who received sodium hyaluronate had an additional time-to- total knee replacement of 217 (±10) days (0.6 years/7.1 months) on average compared to patients who did not receive sodium hyaluronate (p-value<0.0001).

Everything else being equal, the restricted mean survival time and ambulatory care costs were 842 days (95%CI [832,852], 2.3 years) and €744 vs. 625 days (95%CI [605,646], 1.7 years) and €805 for the sodium hyaluronate group and those who were not given sodium hyaluronate, respectively. These costs included intraarticular injections, which represented approximately €60 (hyaluronic acid) and €8 (no hyaluronic acid), respectively. The main strength of the study was the use of real-world data from an administrative claims database, the EGB, which was a representative sample of the entire insured French population. [33]

7.2. Safety

A systematic review was published in 2016. [34] The meta-analyses and/or systematic reviews that compared sodium hyaluronate and placebo for knee osteoarthritis were identified. The systematic review of overlapping meta-analyses demonstrated, that the intraarticular injection of sodium hyaluronate was an effective intervention in treating knee OA without increased risk of adverse events. There was no difference either in the overall or in the individual adverse events' rate. This has been confirmed by other publications as well. [35]

In a systematic review published in 2016, no significant risks of non-serious or serious adverse events were found compared to placebo overall as well as local, joint, and other non-serious or serious adverse events in a stratified analysis. (*Table 6.*) [36]

Table 6. Adverse event analysis [36]

Adverse event category	Number of			Sample size		Rel-ative risk	95 % confidence Interval
	Studies	Events, HA group	Events, Placebo group	HA group	Placebo group		
All serious AEs (combined joint and other*)	8	27	16	1056	1017	1.39	(0.78, 2.47)
Serious AEs, joint (e.g., synovitis)	5	10	8	442	447	1.25	(0.53, 2.94)
Serious AEs, other (e.g., herpes zoster)	6	17	8	614	570	1.52	(0.70, 3.26)
All non-serious AEs (combined joint, local non-joint, and other)	10	415	375	1645	1564	1.03	(0.93, 1.15)
Non-serious AEs, joint (e.g., pain)	7	121	97	559	518	1.15	(0.91, 1.43)
Non-serious AEs, local non-joint (e.g., erythema)	6	98	79	492	493	1.26	(0.99, 1.60)
Non-serious AEs, other (e.g., headache)	6	196	199	594	553	0.89	(0.78, 1.03)

No significant risk of non-serious and serious adverse events associated with hyaluronic acid (HA) injections in knee osteoarthritis (confidence intervals cross 1; italicized rows) have been found. Subgroup analysis by AE category (joint, other, local non-joint) also found no significant risk of NSAEs or SAEs (confidence intervals cross 1; plain text rows) *No studies reported local non-joint SAEs

8 Synolis VA

SYNOLIS VA 40/80 and SYNOLIS VA 80/160, manufactured by Aptissen SA are classified as a Class III medical devices according to Rule 8 of Annex VIII of the European Medical Device Regulation (MDR) 2017/745.

SYNOLIS VA 40/80 has been CE-marked and marketed in Europe since 2009 under the MDD 93/42/EEC, as amended by the directive 2007/47/EC. The CE mark was obtained by Aptissen in 2014. SYNOLIS VA 40/80 is also distributed under the brand name GO-ON® Matrix and HYLASTO S. SYNOLIS VA 80/160 has been CE-marked since 2019.

Performance of SYNOLIS VA in the treatment of symptomatic OA is achieved through high concentration and high mean molecular weight of sodium hyaluronate combined with sorbitol. This unique combination confers to this gel its ability to restore joint lubrication and its shock absorbing properties similar to those of the healthy synovial fluid.

SYNOLIS VA reduces local pain and discomfort caused by symptomatic OA and improves mobility of the synovial joints of the knee and hip (for hip, SYNOLIS VA 80/160 only).

8.1. Clinical Benefits and Therapeutic Effect Duration

Several studies demonstrated that the clinical benefits of SYNOLIS VA can be observed up to 6 months after injection in the knee or the hip (Heisel 2012 [38], Heisel 2013 [39], Migliore 2014 [41], Cortet 2021 [44], Cucurnia 2021 [45], SYMOCA Study [46]). Of note, one study demonstrated that the clinical benefits of SYNOLIS VA can be observed up to 12 months (Migliore 2014 [41]).

The clinical evidence collected on SYNOLIS VA, along with GO-ON Matrix, validated measurable, meaningful, and patient-relevant clinical outcomes as follows:

In terms of pain:

Knee

- 16.8% of the patients were pain-free after the first injection of GO-ON Matrix (same as SYNOLIS VA 40/80), and 40.6% were pain-free 24 weeks after treatment (3 IA injection at 1-week intervals) was initiated. (Heisel 2012).
- Mean decrease in WOMAC pain score between Day 0 and Day 168 in patients treated with one injection of SYNOLIS VA 80/160 in the knee was -29.9 (SD: 23.3). Overall patient Response Rate according to OMERACT-OARSI criteria was 78.9% at day 168. (Cortet 2021).
- Significant decrease in WOMAC pain score 1, 3, and 6 months compared to baseline after one injection of SYNOLIS VA 80/160 in the knee was observed: mean pain score at baseline was 27.6, 20.1 at 1 month, 17.6 at 3 months, 13.9 at 6 months, and 22.3 at 12 months. (Cucurnia 2021).
- Decreased in WOMAC Index Pain from baseline up to Day 84 after treatment with SYNOLIS VA 40/80 (34. 8 [15.0] vs. 15.7 [14.8]) and after treated with SYNOLIS VA 80/160 (42.1 [20.2] vs 11.3 [12.5]). (PMCF2-4mL Study [47])

Knee and hip

- Mean reductions in pain for patients receiving 3 injections of GO-ON Matrix (1.65 points) vs. only 1 injection (1.44 points) was statistically significant (Heisel 2013).

Hip

- Significant decreased in pain VAS compared to baseline (5.7) at 3 months (2.8), 6 months (3.2), 9 months (4.1) and 12 months (2.3). (Migliore 2014)
- A significant decrease in pain was observed at each visit compared to baseline ($p<0.001$). Compared to baseline, mean (SD) decrease in pain VAS was 0.5 (0.7) at 1.5 months, 1.5 (1.3) at 3 months, and 2.5 (1.6) at 6 months. (SYMOCA Study)

In terms of joint mobility:

Knee

- 14.9% of patients complained of severe or very severe functional impairment before treatment, but only 4% after the first injection and only 1% at 24 weeks (Heisel 2012).
- 51.5% of patients had no functional deficit 24 weeks after the beginning of the injection treatment (Heisel 2012).
- Significant score improvement in both stiffness (-22.1) and functions (-27.7) from baseline to Day 168 both in Per Patient (PP) and Intention-to-Treat (ITT) datasets. The WOMAC total score improvement compared to baseline was -27.24 (Cortet 2021).
- 29.1% of patients complained of severe or very severe functional impairment before treatment, but only 3.6% after 3 months, and 3.9% six months after the first injection (Heisel 2013).
- 66.4% of the patients had no or mild impairment at 3 and 6 months after the first injection. (Heisel 2013).
- Greater improvements in functional impairment were observed for patients receiving 2 (1.44 points) or 3 injections (1.13) vs. only 1 injection (0.89) of GO-ON Matrix. (Heisel 2013)
- Significant decrease in WOMAC Stiffness score at 1, 3, and 6 months compared to baseline was observed after one injection of SYNOLIS VA 80/160 in the knee: mean stiffness score at baseline was 5.1, 3.7 at 1 month, 3.3 at 3 months, 2.1 at 6 months, and 6.4 at 12 months (Cucurnia 2021).
- Significant decrease in WOMAC Functional limitation score at 1, 3, and 6 months compared to baseline was observed after one injection of SYNOLIS VA 80/160 in the knee: mean Functional limitation score at baseline was 77.9, 62.3 at 1 month, 55.9 at 3 months, 46.5 at 6 months, and 57.2 at 12 months (Cucurnia 2021).
- Decreased in WOMAC Index Stiffness from baseline up to Day 84 after treatment with SYNOLIS VA 40/80 (2.7 [1.8] vs. 1.5 [1.8]) and after treated with SYNOLIS VA 80/160 (8.5 [3.8] vs 2.3 [2.9]) (PMCF2-4mL Study)
- Decreased in WOMAC Index Function from baseline up to Day 84 after treatment with SYNOLIS VA 40/80 (24.8 [11.2] vs. 11.3 [10.8]) and after treated with SYNOLIS VA 80/160 (30.6 [15.6] vs 8.2 [9.3]) (PMCF2-4mL Study)

In terms of analgesic/NSAIDs intake:

- Significant reduction of NSAIDs taken, from 8/20 patients at baseline to 2, 2, 3 and 1 patient(s) at 3, 6, 9 and 12 months (Migliore 2014).

In terms of disability (scores measuring both pain and joint mobility):

Knee

- Mean decrease in WOMAC total score between Day 0 and Day 168 in patients treated with one injection of SYNOLIS VA 80/160 in the knee was -27.24 (Cortet 2021)

Hip

- WOMAC Total Score was significantly decreased in patient with hip OA treated with a single injection of SYNOLIS VA 80/160 (Mean decrease [SD]: 12.5 [5.3]; p<0.001) at 6-month compared to baseline (SYMOCA study)
- The HSS score significantly increased at 3 months compared to baseline in patients with hip OA treated with a single injection of SYNOLIS VA 80/160 (Mean increase [SD]: 13.3 [10.2]; p<0.001) indicating pain and functionality improvements (SYMOCA study)
- The Lequesne index score decreased significantly from baseline to 12 months (p<0.001) from 5.9 at baseline to 2.6 at 12 months (Migliore 2014).

8.2. Clinical Safety

Through the reviewed literature and PMS data, the following safety/adverse events occurred with the use of SYNOLIS VA and GO-ON Matrix:

Overall, the clinical safety of SYNOLIS VA was assessed in at least 1323 patients.

AEs reported after injection of SYNOLIS VA within clinical studies were:

- Adverse events related “Muskuloskeletal and connective tissue disorders”, not further specified (Cortet 2021)
- Adverse events related to “General disorders and administration-site conditions” not further specified (Cortet 2021)
- Joint effusion/joint effusion at injection site (Heisel 2013, Hungary study [40])
- Joint swelling (Cortet 2021, Hungary study, PMCF2-4mL-Single injection)
- Warmth at injection site/Joint warmth (Heisel 2013/)
- Injection site joint pain/injection site pain (Heisel 2013, Hungary study, PMCF2-4mL-Single injection, SYMOCA study)
- Joint instability (Heisel 2013)
- Transient discomfort (Migliore 2014)
- Worsening of pain and loss of mobility (Hungary study)

The overall frequency of treatment related AE's in different studies was varying between 0,8% and 5,4%. No SAE's were reported.

PMS and Vigilance:

- Allergic reaction
- Inflammatory reaction
- Lack of efficacy (described by only one surgeon).
- Missing product in the box
- Pain
- Swelling
- Risk related to labelling/packaging issue
- Skin rash
- Synovitis symptoms

Most of these AEs are expected AEs according to the State of the Art that remain minor or mild and transient. As such, they are outweighed by the clinical effects and benefits of SYNOLIS VA. In addition, the reactive PMS performed by Aptissen identified few complaints since the first commercialization of SYNOLIS VA (0.0018% of the sold units in 2020, 0.01% and below since first commercialization).

8.3. Device Description

SYNOLIS VA is a viscoelastic, sterile, apyrogenic, isotonic, buffered, 2% solution of sodium hyaluronate. Sodium hyaluronate used in SYNOLIS VA is obtained from bacterial fermentation and presents a high mean molecular weight (MW) of 2 Million Daltons (MDa). SYNOLIS VA has a neutral pH of 6.8 – 7.4, similar to the synovial fluid.

High concentration and MW of sodium hyaluronate combined with a polyol (sorbitol) that limits its degradation confer the ability of this viscoelastic solution to restore joint lubrication and shock–absorbing properties, similar to healthy synovial fluid.

SYNOLIS VA functions by restoring physiological and viscoelastic properties of the synovial fluid, which has been lost progressively during the OA development. Therefore SYNOLIS VA reduces local pain and discomfort caused by symptomatic OA and improves mobility of the synovial joints.

SYNOLIS VA is available in two packaging (see *Table 1*).

Table 1. SYNOLIS VA variants

	SYNOLIS VA 40/80	SYNOLIS VA 80/160
How it is supplied	Pre-filled 2 mL of gel in glass syringe	Pre-filled 4 mL of gel in glass syringe
Indication	Osteoarthritis of the knee	Osteoarthritis of the knee and hips
Composition (for 1 mL)	Sodium hyaluronate: 20 mg Sorbitol: 40 mg Phosphate-buffer qs: 1 mL	Sodium hyaluronate: 20 mg Sorbitol: 40 mg Phosphate-buffer qs: 1 mL

The sterilization method is moist heat.

The packaging includes 1 syringe (*Figure 1*), traceability labels and one instruction leaflet.

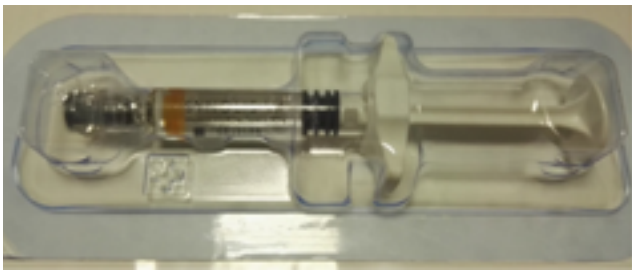


Figure 1. SYNOLIS VA 40/80

8.3.1. Nature and Duration of Contact

SYNOLIS VA is for single-use only.

8.3.2. Body Contact

SYNOLIS VA is in contact with intra-articular cavity tissues and the synovial fluid of the knee and hips (SYNOLIS VA 80/160 only).

8.3.3. Precautions for Use

- Before treatment the patient must be informed about the device, its contra-indications and possible side effects.
- Do not use SYNOLIS VA for any indication other than symptomatic OA,
- In the absence of available clinical data on tolerance and efficacy of SYNOLIS VA in patients with antecedents or active auto-immune disease, or patients with an abnormal physiological condition, the physician must decide whether to inject SYNOLIS VA on a case-by-case basis depending on the nature of the disease as well as the associated concomitant treatments. It is recommended to propose a prior test to these patients and not to inject if the disease is evolving. It is also recommended to carefully monitor these patients after injection.
- Check the integrity of the inner packaging prior to use and check the expiry date. Do not use the product if the expiry date has lapsed or if the packaging has been opened or damaged.
- Do not transfer SYNOLIS VA into another container and do not add other ingredients to the product.
- The IA injection should be performed carefully in order to avoid injecting outside the intra-articular cavity or into the synovial membrane. Viscoelastic gels injected in the peri-synovial area can be painful due to compression on the surrounding tissues.
- It is not recommended to inject into a joint of a limb presenting important venal or lymphatic stasis.
- It is not recommended to inject into an infected or seriously inflamed joint.
- In case of significant joint effusion, the physician must decide whether to inject SYNOLIS VA on a case-by-case basis. Effusion must be aspirated before injecting SYNOLIS VA.
- SYNOLIS VA is a single-use only product, thus it should not be used for several patients and/or different sessions.
- The product must not be resterilised. Reuse of single-use products may cause infections as the sterility is void. Only the gel is sterile but not the outside of the syringe.
- SYNOLIS VA must be administered under strict aseptic conditions.
- The patient is advised to avoid any intense physical activity, including prolonged standing for at least 48 hours after the injection.
- Product must be stored under recommended storage conditions.
- Discard the syringe (and the needle selected by the practitioner) in accordance with accepted medical practice and applicable national, local and institutional requirements.

8.3.4. Contra-indications

SYNOLIS VA must not be:

- injected in patients with known hypersensitivity or allergy to sodium hyaluronate and/or sorbitol preparation,
- injected in patients with a skin disorder or an infection at the site of the injection,
- injected intravascularly,
- injected in pregnant or breast-feeding women,
- injected in young people under the age of 18 years

8.3.5. Side Effects

Possible side effects exist and must be described to the patient before treatment. Slight bleeding may occur during the injection, although it stops spontaneously as soon as the injection is completed. In occasional cases one or more of the following reactions may occur either immediately or as a delayed reaction. It can be temporary local pain, oedema, and/or joint effusion. These reactions usually heal within few days. If these symptoms persist for over a week, or if any other side effects occur, the patient must inform the doctor. The doctor may prescribe appropriate treatment for these undesirable effects. Other possible typical side effects of viscosupplement injections include inflammation, redness, swelling, skin irritation, allergic and tissue reaction. Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.

8.3.6. Drug Interactions

There is a known incompatibility between sodium hyaluronate and quaternary ammonium salts such as benzalkonium chloride. Therefore, SYNOLIS VA must never come into contact with such products (e.g.: certain disinfectants), nor with medical or surgical equipment treated with these types of products. To date, no data is available on the compatibility of SYNOLIS VA with other products for intra-articular use.

8.3.7. Instructions for Use (IFU) - Information Supplied with the Device

Description

Synolis VA is a viscoelastic, sterile, apyrogenic, isotonic, buffered, 2% solution of sodium hyaluronate. Sodium hyaluronate used in Synolis VA is obtained from bacterial fermentation and presents a high mean molecular weight (MW) of 2 MDa. Synolis VA has a neutral pH of 6.8 – 7.4 similar to the synovial fluid. High concentration and MW of sodium hyaluronate combined with a polyol (sorbitol) that limits its degradation confer the ability of this viscoelastic solution to restore joint lubrication and shock–absorbing properties, similar to healthy synovial fluid. Synolis VA functions by restoring physiological and viscoelastic properties of the synovial fluid which has been lost progressively during the osteoarthritis (OA) development. Therefore Synolis VA reduces local pain and discomfort caused by symptomatic OA and improves mobility of the synovial joints.

Introduction

Synolis VA is available in two packaging. Those packaging include 1 syringe, traceability labels and one instruction leaflet. An implantcard to be filled by the practitioner for the patient is availa ble with each product.

SYNOLIS VA 40/80	SYNOLIS VA 80/160
pre-filled 2ml of visco-antalgic gel in glass syringe	pre-filled 4ml of visco-antalgic gel glass syringe

Composition

Ingredients	For 1 mL
Sodium hyalurnate	20 mg
Sorbitol	40 mg
Phosphate-buffer qs	1 ml

The terilisation method is moist heat.

Indications

Synolis VA is indicated for treatment of symptomatic osteoarthritis (OA), in order to reduce pain and improve mobility following degenerative changes in the synovial joints:

SYNOLIS VA 40/80	SYNOLIS VA 80/160
Knee	Knee and hips

This treatment responds to patient who failed to conservative nonpharmacologic therapy and simple analgesics and/or NSAIDs or who have intolerance to simple analgesics and/or NSAIDs.

Dosage and method of administration

The treatment must be adapted depending on patient radiological and physical state (Kellgren Lawrence grade, pain and mobility). Available clinical data have demonstrated performance of different injection regimen based on the severity of osteoarthritis:

Injection regimen / Severity	Low to moderate severity	Moderate to serious severity
1 injection of SYNOLIS VA 40/80	✓	
1 Injection of SYNOLIS VA 80/160	✓	✓
3 injections of SYNOLIS VA 40/80 weekly apart.		✓

An additional injection of SYNOLIS VA may be performed when OA symptoms resume or for maintaining local pain management and joint function. However, treatment benefits are expected to last for a minimum of 6 months for responding patients.

The time period before repeating the treatment regimen depends also on physician's experience and/or severity of the affection.

SYNOLIS VA should be injected within the synovial cavity by a physician skilled in performing intra-articular (IA) injections.

Several actions should be taken prior to inject SYNOLIS VA:

- SYNOLIS VA gel should be at room temperature at the moment of the IA injection,
- The injection site must be carefully disinfected,
- Appropriate size of the needle must be selected by the practitioner (recommendation for injection in the knee joints: 18 to 21 G)
- Appropriate size of the needle must be used (recommendation for injection in the knee joints: 18 to 21 G)
- The needle must be firmly attached to the luer lock collar of the syringe,
- Inject accurately into the joint cavity only.

Contra indications

SYNOLIS VA must not be :

- injected in patients with known hypersensitivity or allergy to sodium hyaluronate and/or sorbitol preparation,
- injected in patients with a skin disorder or an infection at the site of the injection,
- injected intravascularly,
- injected in pregnant or breast feeding women,
- injected in young people under the age of 18 years.

Precautions for use

- Before treatment the patient must be informed about the device, its contra-indications and possible side effects.
- Do not use SYNOLIS VA for any indication other than symptomatic OA,
- In the absence of available clinical data on tolerance and efficacy of SYNOLIS VA in patients with antecedents or active auto-immune disease, or patients with an abnormal physiological condition, the physician must decide whether to inject SYNOLIS VA on a case-by-case basis depending on the nature of the disease as well as the associated concomitant treatments. It is recommended to propose a prior test to these patients and not to inject if the disease is evolving. It is also recommended to carefully monitor these patients after injection.
- Check the integrity of the inner packaging prior to use and check the expiry date. Do not use the product if the expiry date has lapsed or if the packaging has been opened or damaged.
- Do not transfer SYNOLIS VA into another container and do not add other ingredients to the product.
- The IA injection should be performed carefully in order to avoid injecting outside the intra-articular cavity or into the synovial membrane. Viscoelastic gels injected in the peri-synovial area can be painful due to compression on the surrounding tissues.
- It is not recommended to inject into a joint of a limb presenting important venal or lymphatic stasis.
- It is not recommended to inject into an infected or seriously inflamed joint.
- In case of significant joint effusion, the physician must decide whether to inject SYNOLIS VA on a case-by-case basis. Effusion must be aspirated before injecting SYNOLIS VA.
- SYNOLIS VA is a single-use product, thus it should not be used for several patients and/or different sessions.
- The product must not be resterilised. Reuse of single-use products may cause infections as the sterility is void. Only the gel is sterile but not the outside of the syringe.
- SYNOLIS VA must be administered under strict aseptic conditions.
- The patient is advised to avoid intense physical activity for at least 48 hours after the injection.
- Product must be stored under recommended storage conditions.
- Discard the syringe (and the needle selected by the practitioner) in accordance with accepted medical practice and applicable national, local and institutional requirements.

Drug interactions

There is a known incompatibility between sodium hyaluronate and quaternary ammonium salts such as benzalkonium chloride. Therefore, SYNOLIS VA must never come into contact with such products (e.g.: certain disinfectants), nor with medical or surgical equipment treated with these types of products. To date, no data is available on the compatibility of SYNOLIS VA with other products for intra-articular use.

Side effects

Possible side effects exist and must be described to the patient before treatment. Slight bleeding may occur during the injection, although it stops spontaneously as soon as the injection is completed. In occasional cases one or more of the following reactions may occur either immediately or as a delayed reaction. It can be temporary local pain, oedema, and/or joint effusion. These reactions usually heal within few days. If these symptoms persist for over a week, or if any other side effects occur, the patient must inform the doctor. The doctor may prescribe appropriate treatment for these undesirable effects. Other possible typical side effects of viscosupplement injections include, inflammation, redness, swelling, skin irritation, allergic and tissue reaction. Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.

Storage

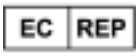
Store between 2 and 25 C. Protect from light and extreme cold. Do not freeze the product.

Manufacturer

Aptissen SA.
Chemin du Champ des Filles 36,
1228 Plan-les-Ouates,
Switzerland
Tel: +41 (0) 22 552 21 21
Email : support@aptissen.com

www.aptissen.com

Explanation of used symbols

Manufacturer	5.1.1	
EU representative	5.1.2	
Date of manufacture	5.1.3.	
Batch code	5.1.5.	
Use by date	5.1.4.	
Sterilised using steam	5.2.5.	
Single sterile barrier system with protective packaging outside	5.2.14	
Do not resterilise	5.2.6.	
Do not reuse	5.4.2.	
Do not use if package is damaged	5.2.8.	
Keep away from sunlight	5.3.2.	
Keep dry	5.3.4.	
Temperature limit	5.3.7.	
Medical Device	5.7.7	
Unique Device Identifier	5.7.10	
Consult instructions for use	5.4.3	
Caution	5.4.4.	
CE marking in compliance with the regulation 2017/745 relating to medical device	5.4.5.	

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