SUMMARY OF SAFETY AND CLINICAL PERFORMANCE (for users/healthcare professionals)

VISCO-SUPPLETIVE JOIN DEVICE

0.8% - 8 mg / 1 ml hyaluronic acid sodium salt (Mini)

0.8% - 16 mg / 2 ml hyaluronic acid sodium salt

1.6% - 32 mg / 2 ml hyaluronic acid sodium salt (Forte/Highvisc)

2.0 % - 50 mg / 2.5 ml hyaluronic acid sodium salt (One/Once)

With the following brand names:

Sinovial

Intragel

Gony Alert MD

Jointex 1

in accordance with Medical Device Regulation (EU) 2017/745 and MDCG 2019-9

Manufacturer

IBSA Farmaceutici Italia Srl

Via Martiri di Cefalonia 2, 26900, Lodi, Italy

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients. The following information is intended for ***users/healthcare professionals****.*

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1. *Device identification and general information*

1.1. Device trade name(s)

"VISCO-SUPPLETIVE JOINT DEVICE" with the following concentrations:

- 0.8% - 8 mg / 1 ml hyaluronic acid sodium salt (Mini)
- 0.8% - 16 mg / 2 ml hyaluronic acid sodium salt
- 1.6% - 32 mg / 2 ml hyaluronic acid sodium salt (Forte/Highvisc)
- 2.0 % - 50 mg / 2.5 ml hyaluronic acid sodium salt (One/Once)

Can be marketed with the following brand names:

- INTRAGEL MINI – SINOVIAL MINI – GONY ALERT MD MINI
- INTRAGEL – SINOVIAL – SINOVIAL 16 - GONY ALERT MD
- INTRAGEL FORTE – SINOVIAL FORTE – SINOVIAL 64 - GONY ALERT MD FORTE
- INTRAGEL ONE – SINOVIAL ONE – SINOVIAL 50 - GONY ALERT MD ONE - INTRAGEL ONCE – SINOVIAL ONCE – GONY ALERT MD ONCE – JOINTEX 1

1.2. Manufacturer's name and address

The Manufacturer of this device is:
IBSA Farmaceutici Italia Srl
Via Martiri di Cefalonia 2, 26900, Lodi, Italy

1.3. Manufacturer's single registration number (SRN)

The Manufacturer's single registration number (SRN) is IT-MF-000008111.

1.4. Basic UDI-DI

The basic UDI, for this medical devices, as reported in Declaration of Conformity, are the following:

- for the pre-filled syringe only is 803363895IA0034V
- for the kit is 803363895IAK0036B

1.5. Medical device nomenclature description / text

The CND for "VISCO-SUPPLETIVE JOINT DEVICE" is P900402.

1.6. Class of device

"VISCO-SUPPLETIVE JOINT DEVICE" has been classified according to the rules 8 of Annex VIII of Regulation EU 2017/745 as Class III.

1.7. Year when the first certificate (CE) was issued covering the device

The first certificate has been issued in 2010. At the Date of Application (DoA) of the MDR, 26th May 2021, the Medical Device "VISCO-SUPPLETIVE JOINT DEVICE" was covered by the following certificates:

- EC design-examination certificate n. EPG-0097-18, dated 26.04.2018
- Full Quality assurance system certificate n. QCT-0043-17, addendum n. 01-18 dated 26.04.2018

both issued by the Notified Body ISS (CE0373) in accordance with Directive 93/42/EEC prior to 25 May 2017 and valid until 04.06.2022.

As per MDR, Art. 120(3), starting from 26.05.2021 (DoA), the Device "VISCO-SUPPLETIVE JOINT DEVICE" is intended to be a Legacy Device, because is a Device lawfully placed on the market pursuant to Directive 93/42/EEC, which may continue to be placed on the market until 04.06.2022 (the end of the period indicated on the MDD-CE certificates).

1.8. Authorised representative if applicable; name and the SRN

N.A. – Not Applicable

1.9. NB's name (the NB that will validate the SSCP) and the NB's single identification number

Eurofins 0477

2. Intended use of the device

2.1. Intended purpose

"VISCO-SUPPLETIVE JOINT DEVICE" is a medical device designed to integrate the synovial fluid, which allows restoring the physiological and rheological properties of arthritic joints and, only for 0.8%, tendons. "VISCO-SUPPLETIVE JOINT DEVICE" reduces pain in the joint and encourages recovery of the associated joint and, for 0,8% tendon mobility, acting only in the synovial cavity into which it is injected.

2.2. Indication(s) and target population(s)

"VISCO-SUPPLETIVE JOINT DEVICE" is a substitute for the synovial fluid, which allows restoring the physiological and rheological properties of arthritic joints. Restoring the viscoelastic properties of the synovial fluid, "VISCO-SUPPLETIVE JOINT DEVICE" is indicated in case of pain or reduced mobility due to degenerative affections (e.g. arthrosis), post-traumatic disorders or joint and, only for 0.8%, tendon

alterations (e.g. acute and chronic tendinopathy) of the large and, only for 0.8%, small joints. “VISCO-SUPPLETIVE JOINT DEVICE” reduces pain and restores joint and tendon mobility.
“VISCO-SUPPLETIVE JOINT DEVICE” is indicated for adults of both sexes and is to be administered by intra-articular injection by qualified personnel only.

2.3. Contraindications and/or limitations

“VISCO-SUPPLETIVE JOINT DEVICE” must not be injected in the presence of an infected or seriously inflamed joint or if the patient has a cutaneous disease or an infection in the area of the injection site.

3. Device description

3.1. Description of the device

“VISCO-SUPPLETIVE JOINT DEVICE” is a substitute for the synovial fluid, which allows restoring the physiological and rheological properties of arthritic joints. This therapeutic action is expressed by the particular characteristics of the hyaluronic acid used. “VISCO-SUPPLETIVE JOINT DEVICE” is composed of a buffered saline solution of hyaluronic acid sodium salt with viscoelastic properties, obtained by fermentation and not chemically modified, and has excellent tolerability. Restoring the viscoelastic properties of the synovial fluid, “VISCO-SUPPLETIVE JOINT DEVICE” reduces pain and restores joint and, only for 0.8%, tendon mobility. “VISCO-SUPPLETIVE JOINT DEVICE” acts only in the area where it is injected without any systemic action. “VISCO-SUPPLETIVE JOINT DEVICE” contains 0.8%, 1.6% and 2.0% highly purified hyaluronic acid sodium salt with a molecular weight between 800 and 1.200 KDalton. Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate and is an essential component of the synovial fluid giving it particular viscoelastic properties.

3.2. A reference to previous generation(s) or variants if such exist, and a description of the differences

The product has not previous generation or variant.

3.3. Description of any accessories which are intended to be used in combination with the device

The device is not intended to be used with any accessory.

3.4. Description of any other devices and products which are intended to be used in combination with the device

The device is intended to be used with needles and it can be placed on the market as a single syringe or a system, that is in combination with other device as following:

- INTRAGEL MINI – SINOVIAL MINI – GONY ALERT MD MINI - 0.8% - 8 mg/1 ml Hyaluronic Acid Sodium Salt – available in kit of 1, 3 or 5 syringes with needle/s 21 G x ½ "
- INTRAGEL – SINOVIAL – SINOVIAL 16 - GONY ALERT MD - 0.8% - 16 mg/2 ml Hyaluronic Acid Sodium Salt – available in kit of 1, 3 or 5 syringes with needle/s 21 G x ½ "
- INTRAGEL FORTE – SINOVIAL FORTE – SINOVIAL 64 - GONY ALERT MD FORTE - 1.6% - 32 mg/2 ml Hyaluronic Acid Sodium Salt – available in kit of 1, 3 or 5 syringes with needle/s 21 G x ½ "
- INTRAGEL ONE – SINOVIAL ONE – SINOVIAL 50 - GONY ALERT MD ONE - INTRAGEL ONCE – SINOVIAL ONCE – GONY ALERT MD ONCE – JOINTEX 1 - 2.0% - 50 mg/2.5 ml Hyaluronic Acid with needle/s 21 G x ½ "

4. Risks and warnings

4.1. Residual risks and undesirable effects

According to Risk Assessment, it is possible to state that "VISCO-SUPPLETIVE JOINT DEVICE" Residual Risks are intrinsic and cannot be further reduced and the Overall Residual Risk can be considered as acceptable. For these reasons, "VISCO-SUPPLETIVE JOINT DEVICE" Residual Risks are acceptable if compared with its Benefits hence the Benefit/Risk ratio can be considered as positive. According to Risk Assessment, however, the following side-effects and adverse events must be reported on IFU – Instructions for Use:

Side-effects:
Extra-articular seepage of Risk Assessment may cause undesirable effects locally. During the use of "VISCO-SUPPLETIVE JOINT DEVICE", symptoms such as pain, the sensation of heat, reddening or swelling may appear at the injection site. These secondary manifestations can be relieved by applying ice on the treated area. They generally disappear in a short period of time. Physicians/specialists must ensure that patients notify them of any undesirable effects which occur after the treatment.
In case of incident, inform the Manufacturer or the Competent Authority.

Post-market experience of the cumulative period, June 2005 -the date of the launch of the product- to December 2020 showed a very low incidence (0,005%) of adverse events (AEs) taking into account the cumulative patient exposure (a total of 3.211.089 exposed patients): 79 cases (3 incidents) describing a total of 162 AEs have been collected by IBSA.

The expected adverse events that can be potentially attributed (or only in part) to the product (i.e. adverse reactions), are injection site reactions (ISRs) ie, pain, swelling, erythema, bruising. These AE are generally mild (occasionally moderate in severity) and transient (not more than 7 days), do not require any medication (except cold ice or a simple analgesic) and the product can be safely repeated to complete the scheduled cycle. It is not possible to determine if the ISR is related to procedure (the injection itself)

or the action of the solution injected (local hypersensitive reaction). When the AE is immediate, this is considered to be procedure-related, when the time to onset is > 24-48 hours a local hypersensitivity reaction is more likely involved.
The analysis of the AE is in line with the product profile: local signs or symptoms of pain and inflammation (redness, swelling, heating) or intolerance/allergy emerging following injection (1-2 days). They may be considered flare-ups of the underlying disorder (knee osteoarthritis) triggered by the intra-articular injection.

Contra-indications:
"VISCO-SUPPLETIVE JOINT DEVICE" must not be injected in the presence of an infected or seriously inflamed joint or if the patient has a cutaneous disease or an infection in the area of the injection site.

4.2. Warnings and precautions

- The content of the prefilled syringe is sterile.
- The syringe is packed in a sealed blister pack. - The outer surface of the syringe is not sterile.
- Do not use "VISCO-SUPPLETIVE JOINT DEVICE" after the expiry date indicated on the package.
- Do not use "VISCO-SUPPLETIVE JOINT DEVICE" if the packaging is open or damaged.
- The injection site must be on healthy skin.
- Do not use in pregnant or breast-feeding women.
- Do not use in patients with autoimmune diseases.
- Do not inject intravascularly. Do not inject outside the joint cavity, into the synovial tissue or into the articular capsule.
- Do not administer "VISCO-SUPPLETIVE JOINT DEVICE" in the presence of heavy intra-articular effusion.
- Do not resterilize. The device is intended for single use only.
- Do not reuse in order to prevent any risk of contamination.
- Store at ambient temperature below 25°C and away from heat sources. Do not freeze.
- Once opened, "VISCO-SUPPLETIVE JOINT DEVICE" must immediately be used and discarded after use.
- "VISCO-SUPPLETIVE JOINT DEVICE" is indicated for adult patients.
- Keep out of the reach and sight of children.
- Do not use "VISCO-SUPPLETIVE JOINT DEVICE" in case of known hypersensitivity or allergies to the components of the product.
- After injection, advise the patient to avoid any intense physical activity and to resume his or her normal activities only after several days.
- Any air bubble present does not compromise the characteristics of the product.

4.3. Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN) if applicable

No Field Safety Corrective Actions and Field Safety Notices have ever been required.

5. *Summary of clinical evaluation and post-market clinical follow-up (PMCF)*

In order to confirm the efficacy and safety of the product, several studies have been conducted with SINOVIAL (0,8%, 1,6%, 2%) for the treatment of osteoarthritis and tendinopathies.

5.1. *Summary of clinical data related to equivalent device, if applicable*

Several similar devices are available on the market but none of them can be considered fully equivalent with SINOVAL. Therefore, no clinical data related to equivalent device has been evaluated.

5.2. *Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable*

The following studies have been performed on the SINOVIAL 0.8% (2 ml) still marketed under the Directive 93/42/EEC.

- *K. Pavelka, D. Uebelhart. Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial®) vs hylan G-F20 (Synvisc®) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel group non inferiority study. Osteoarthritis &Cartilage 2011; 19 (11): 1294-1300.*

Reference to the clinical trial /database	NCT00556608 (ClinicalTrials.gov Identifier).
Countries (if extra EU) where the study was conducted	Czech Republic
Intended use of the Medical device used in the investigation	The product was used for the treatment of knee osteoarthritis.
Objectives of the study	This study was conducted to demonstrate the non-inferiority of the highly purified intra-articular injection of hyaluronic acid (SINOVIAL 0.8% (16 mg/2ml)) in comparison to Hylan G-F20 (Synvisc) in the treatment of knee osteoarthritis.
Study design	This study is a phase III, double-blind (patient and observer blinded,) multicentre, randomised, non-inferiority study.
Endpoints	The primary efficacy variable was change from baseline in Western Ontario and McMaster Universities (WOMAC) Index pain subscore at 26 weeks. Change from baseline in the WOMAC total score, and in the pain, stiffness and function subscores were assessed as secondary efficacy variables. Changes from

	baseline were also assessed for the Lequesne Algofunctional Index, patient assessment of global pain and patient assessment of global status scored on a 0-100 mm VAS, with 0 representing very poor global status and 100 very good global status. Additional secondary efficacy variables were Global Status assessed by Investigator (scored on a 5-point scale, with 0 being very poor and 4 being very good)., Percentage Sum of the Pain Intensity Differences (SPID%) calculated on the basis of weekly assessment of global pain over the 6-month study period, paracetamol consumption for target knee osteoarthritis and overall response rate based on OMERACT-OARSI criteria (at 12 and 26 weeks). Patient assessment of treatment satisfaction was also evaluated. Secondary safety endpoints included: Adverse Events (AEs), pain at injection site immediately after the injection and local tolerability (assessed by patient and Investigator on a 5-point scale with: 0 being very poor and 4 being very good).
Inclusion and exclusion criteria	Included patients were outpatients aged between 40 and 81 years with symptomatic primary knee osteoarthritis, with symptoms present in the target knee for at least 3 months. All patients were required to have an American Colleague of Rheumatology (ACR) clinical and radiological-based diagnosis of target-knee osteoarthritis, and Kellgren & Lawrence grade 2-3 osteophytes within 6 months of screening. Included patients were those who had failed to respond sufficiently to analgesics and/or Non- steroidal Antirheumatic Drugs (NSAIDs) taken regularly, or those who responded but who were unable to tolerate such treatment. Mean WOMAC pain subscore at the target knee was required to be ≥40mm and <80 mm on a 100 mm visual analog scale (VAS) following NSAIDs/analgesic washout, with mean WOMAC pain subscore <30 mm on a 100 mm VAS in the contralateral knee. Patients were excluded due to: Body Mass Index (BMI) ≥ 32 kg/m2, secondary target knee osteoarthritis, predominantly femoral-patella knee pain mainly related to femoral patellar syndrome at the target knee, no remaining joint space width at the target knee, symptomatic hip osteoarthritis or other condition that would interfere with study assessments, severe varus/valgus deformity in the target knee, history or current evidence of other joint diseases (inflammatory, infective or metabolic joint disease), concomitant rheumatic disease, significant injury to the target knee in the past 6 months, previous joint replacement or arthroplasty on the target knee, arthroscopy, osteotomy or surgery on the target knee in the past year, any surgical procedure scheduled in the next 6 months, venous or lymphatic stasis in the relevant limb, skin infection, disease or trauma at the injection site, systemic or intra-articular (target knee) corticosteroids in the past 3 months, intra-articular corticosteroids (contralateral knee) in the past 4 weeks, viscosupplementation to the target knee in the past year, initiation of target knee physical therapy in the past 3 months, initiation/change in dose of symptomatic slow-acting drugs for osteoarthritis therapy, ongoing anticoagulant therapy, chronic/recurrent use of NSAIDs, analgesics or narcotics other than for osteoarthritis of the target knee, history of allergy or hypersensitivity to hyaluronic acid, paracetamol or avian proteins, participation in a clinical study within the past 3 months, pregnant or

	lactating women, and women of childbearing potential not willing to use adequate contraception.
Number of enrolled patients	A total of 381 patients were randomized at the 23 sites, all but one received at least one intra-articular injection of the assigned hyaluronic acid preparation. Two populations were analysed: - ITT population, the all 380 patients who received at least one injection of SINOVIAL or Synvisc, with two patients in the SINOVIAL group not receiving a second and third injection, compared with three and five Synvisc patients. Overall, 99.0% of the SINOVIAL group and 97.3% of those assigned to Synvisc were given all three injections. - PP population, which excluded 27 patients with serious protocol violations.
Study population	The average age of the 380 ITT patients was 65 years (range 41.8-80.9), the majority were female (72.9%) and the predominant prior/ongoing medical condition was hypertension. Patient-assessed global pain scores at screening and baseline aver aged 65.3 and 65.6, respectively (on a 100-point scale), while other indices of disease severity were also suggestive of mild to moderate target knee osteoarthritis.
Summary of the study methods	Eligible patients were assigned a three-digit randomisation number for identification purposes. Patients were given a 1-month supply of rescue medication and requested not to consume this within the 24 h prior to visits. Rescue medication use was to be recorded in a patient diary, along with concomitant medication usage, adverse events, lifestyle changes and the weekly global pain assessment. Patients were randomised to receive once weekly for 3 weeks either 16 mg/2 ml (0.8%) SINOVIAL or 16 mg/2 ml (0.8%) of intra-articular hylan G-F20, a cross-linked polysaccharide chain containing hylan A with a mean MW of 6,000 kDa and hylan B a hydrated gel, Synvisc. Control visits were carried out at 4, 12 and 26 weeks.
Summary of results	Both the preparations proved to be equally effective in improving clinical performance as demonstrated by multiple outcome measures. There were no statistically significant differences between groups at 26 weeks, although Sinovial-treated patients tended to have a slightly better outcome for select variables, as they did at earlier time-points, some of which reached statistical significance. The safety data collected are largely unremarkable: individual injections were generally well-tolerated, and patient/investigator scoring for global tolerability indicate a widespread procedural acceptability. There were no statistically significant intergroup differences in the overall incidence of adverse events or in severe, serious or suspected treatment-related AEs.

Limitations	A limitation could be the lack of a placebo arm, but it must be considered that use of an intra-articular placebo in trials presents several problems: first, there are ethical concerns using an invasive procedure; second, there are methodological challenges involved in achieving a true placebo when it is necessary to perform arthrocentesis and substitute synovial fluid with saline. For these reasons, it was considered appropriate to assess the test product in terms of non-inferiority to a marketed product, with an already demonstrated effectiveness and Synvisc was chosen as a reference product because in recent meta-analyses it displayed the greatest effect size.

- *Theiler R, Brühlmann P. Overall tolerability and analgesic activity of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Curr Med Res Opin. 2005 Nov;21(11):1727-33.*

Countries (if extra EU) where the study was conducted	Zurich, Switzeralnd
Intended use of the Medical device used in the investigation	Symptomatic knee osteoarthritis
Objectives of the study	The aim of the present study was to investigate the safety and tolerability profile of SINOVIAL 0.8% (2ml) in patients with symptomatic knee OA over 24 weeks
Study design	This was a longitudinal, prospective, single group open label observational study of intra-articular sodium hyaluronate over 24 weeks.
Endpoints	The primary endpoint was to investigate the tolerability and safety profile of intraarticular HA based on spontaneous AE reporting by the patient during the injection session and at any time during the study. The nature, time of onset, duration, severity and relationship to treatment of these AEs were recorded at each visit by the investigator. In addition, haematology (Hb, Ht, RBC, WBC with differential, platelets), blood chemistry (ESR, GT, BUN, bilirubin, creatinine) and urinalysis parameters were recorded at baseline (week 0) and one week after the last injection (week 6). The secondary endpoint was the evaluation of the treatment effects of intra-articular HA based on a self-administered WOMAC OA Index Questionnaire, at each visit. In addition, both the investigator and the patient were asked for an efficacy judgment (by a four-point scale: excellent, good, fair or nil).

Inclusion and exclusion criteria	Included patients were patients aged between 18 and 85 years with confirmed primary or secondary (including post-traumatic) symptomatic knee OA, confirmed by a radiography not older than 12 months, with a Kellgren and Lawrence radiographic grade of II–IV. Patients were included if pain on walking was higher than 30 mm on a 0–100 mm visual analogue scale (VAS), while no analgesics had been taken in the preceding 24 hours. Patients were excluded if they presented symptomatic chondrocalcinosis (pseudogout), crystal arthropathies (i.e. uric acid), acute synovitis or excessive joint effusion (> 100 ml), severe axis deviations (> 15°), joint prosthesis at the target knee, rheumatoid arthritis or other inflammatory diseases (i.e. ankylosing spondylitis), metabolic diseases of the bone (i.e. Paget disease or severe osteoporosis), symptomatic hip OA, history of knee operation or prior arthroscopy within 6 months, intra-articular injection of corticosteroids in the last 3 months prior to testing or chronic daily steroid therapy.
Number of enrolled patients	63 patients of both genders.
Study population	Patients of both genders, (26 M and 36 F), 60+/-12 (range 12-83) years with confirmed primary and secondary (including post-traumatic) symptomatic knee.
Summary of the study methods	After a run-in phase of 1 week with a pharmacological washout HA was injected intra-articularly, once weekly for 5 consecutive weeks; thereafter, the patients were followed-up for an additional 19 weeks with control visits at week 6, 12, 18 and 24. The patients had to answer an AE questionnaire and the WOMAC OA Index questionnaire at each visit. HA was provided as ready-to-use, single-dose syringes containing 16mg of highly purified, chemically non-modified, sodium hyaluronan of mean MW of 1000 kDa.
Summary of results	The WOMAC total score was significantly reduced at baseline after two injections (week 2) and continuous decrease was observed until the end of the active treatment phase. This treatment effect and the WOMAC total score was sustained at the end of the observation period, 24 weeks after treatment initiation. The WOMAC subscores were significantly decreased after 4 weeks of treatment for pain and after 6 weeks for stiffness and physical function, and reported in the observation period, i.e. over 24 weeks after treatment initiation. The evaluation of treatment efficacy was highly consistent between the investigators and the patients. The intra-articular treatment of SINOVIAL was generally well tolerated and no serious treatment adverse events was reported. The most frequent adverse event was pain at the injection site.
Limitations	This study has the limitations of being an open label study of relatively short duration.

5.3. Summary of clinical data from other sources, if applicable

The following studies have been conducted on the products SINOVIAL 0.8% (1ml and 2 ml), 1.6%, 2% still marketed under the Directive 93/42/EEC. For all these studies, a brief summary is reported below.

SINOVIAL 0.8 % (1 ml)

- *Guarda-Nardini L, Rossi A, Ramonda R, Punzi L, Ferronato G, Manfredini D. Effectiveness of treatment with viscosupplementation in temporomandibular joints with or without effusion. International journal of oral and maxillofacial surgery, 2014, Vol. 43, Issue 10, 1218-1223*
  The efficacy of viscosupplementation with SINOVIAL 0.8%, 1 ml, was evaluated in 25 patients with a clinical diagnosis of chronic painful temporomandibular joint (TMJ) osteoarthritis and magnetic resonance imaging (MRI) signs of degeneration of the TMJ, with evidence of TMJ effusion (effusion group) or without (no effusion group). All patients underwent five weekly single-needle arthrocenteses plus SINOVIAL and 6 months follow-up.
  Both groups showed significant improvements in all parameters, which were then maintained at the 6-month follow-up. The reported results show that in a population of patients with TMJ degenerative disorders without psychosocial impairment, the presence of MRI signs of intra-articular effusion did not affect the efficacy of a five-session joint viscosupplementation treatment protocol immediately after lavage.
- *Guarda-Nardini L, Cadorin C, Frizziero A, Masiero S, Manfredini D. Interrelationship between temporomandibular joint osteoarthritis (OA) and cervical spine pain: Effects of intra-articular injection with hyaluronic acid. Cranio. 2016 Sep;35(5):276-282*
  This study was intended to evaluate the pain and function of the cervical spine of 49 patients with TMJ osteoarthritis and concomitant cervical pain and limited cervical function All patients underwent a cycle of five weekly arthrocentesis and viscosupplementation with SINOVIAL 1 ml, according to the single-needle arthrocentesis technique. The outcomes, TMJ pain (VAS), cervical active ranges of motion, cervical disability (NPDS), and presence of painful palpation sites were assessed at baseline, and one, three and 6 months after the treatment.
  Most parameters of active cervical range of motion improved with time and benefits remained stable 6 months after the treatment. The results show that a protocol of TMJ intra articular arthrocentesis and viscosupplementation improved cervical function and reduced disability in patients with concurrent cervical spine pain.
- *Guarda-Nardini L, Cadorin C, Frizziero A, Ferronato G, Manfredini D. Comparison of 2 hyaluronic acid drugs for the treatment of temporomandibular joint osteoarthritis. J Oral Maxillofac Surg. 2012;70(11):2522-30*
  This study aimed to compare the effectiveness of 2 treatment protocols providing 5 weekly temporomandibular joint (TMJ) arthrocenteses immediately followed by injections of 2 different molecular weight hyaluronic acid (HA) drugs, in 40 patients with inflammatory-degenerative TMJ disease, classified in 2 study groups, receiving either low– or medium–molecular weight HA after arthrocentesis. The level of maximum pain at chewing has been

considered as primary outcome variable, and maximum pain at rest, subjective chewing efficiency, functional limitation, treatment tolerability, perceived treatment effectiveness, and jaw range-of-motion function in millimeters were the secondary outcomes. The variables were assessed at the end of treatment, and 3 months later.

After the follow-up period, all the outcome variables improved in both groups of patients. The results show that there are no significant differences for any of the outcome variables: pain at chewing, pain at rest, chewing efficiency, functional limitation, and mouth opening and no differences were shown for perceived treatment effectiveness and treatment tolerability.

- *Roux C, Fontas E, Breuil V, Brocq O, Albert C, Euller-Ziegler L. Injection of intra-articular sodium hyaluronidate (Sinovial) into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis. A prospective evaluation of efficacy. Joint Bone Spine 2007; 74: 368-372*

  The aim of this study was to investigate the pain relief efficacy and function of one, two or three injections of intra-articular hyaluronic acid in symptomatic osteoarthritis of the carpometacarpal joint of the thumb (CMCJ) to find any difference in efficacy at three months on pain and function, in 40 subjects with symptomatic OA of the CMCJ. Each subject was randomly allocated to receive1 (group 1) or 2 (group 2) or 3 injections (group 3) of 1 ml of SINOVIAL, at weekly intervals. In this study, no significant differences were found between each group over the study period for pain relief and function. The results of the intra groups analysis show that intra-articular sodium hyaluronidate injections into the carpometacarpal joint of the thumb in osteoarthritis can be efficacious on pain and functionality, as early as the first month with persistent effects at 3 months.

- *L Guarda-Nardini, A Rossi, R Arboretti, S Bonnini, E Stellini, D Manfredini. Single- or multiple-session viscosupplementation protocols for temporomandibular joint degenerative disorders: a randomized clinical trial. Journal of oral rehabilitation, 2015, 42(7), 521-528*

  The aim of the study was to compare the effectiveness of two single-session protocols, either adopting high- (protocol A) or medium-molecular weight hyaluronic acid (protocol B), with the reference of five-session protocol of temporomandibular joint (TMJ) lavage plus viscosupplementation (protocol C) in the management of chronic TMJ degenerative disorders, with multiple observation points, ending at 6 months after treatment.

  Pain levels on a 10-point VAS scale were selected as the primary outcome variable to rate treatment effectivenessIn conclusion, the standard of reference five-session protocol proved to be superior at 6 months in pain levels decreasing, while there were no differences between the two single-session interventions. The three protocols did not provide any different treatment effect as for some other secondary clinical outcome variables (i.e. perceived subjective efficacy, mouth opening) assessed in this investigation.

- *Manfredini D., Favero L., Michieli M., Salmaso L., Cocilovo F., Guarda-Nardini L. An assessment of the usefulness of jaw kinesiography in monitoring temporomandibular disorders: Correlation of treatment-related kinesiographic and pain changes in patients receiving temporomandibular joint injections. J Am Dent Assoc. 2013; 144 (4): 397-405*

This study aimed to assess whether treatment-related changes in pain levels and chewing ability coincide with a change in jaw kinesiographic (KG) parameters in 34 selected patients with temporomandibular joint (TMJ) osteoarthritis. The patients were underwent a cycle of five weekly arthrocentesis procedures with injections of 1 ml of hyaluronic acid (SINOVIAL).
The authors reported no significant changes in any KG variables, in clinical and KG parameters during the treatment period. Treatment-related changes in pain levels and chewing ability in patients with TMJ osteoarthritis do not coincide with changes in KG parameters.
First of all, these results confirmed the effectiveness of SINOVIAL in reducing symptoms of TMJ osteoarthritis, but suggested that jaw KG is not useful to monitor the disease.

- *Callegari L, Spanò E, Bini A, Valli F, Genovese E, Fugazzola C. Ultrasound-guided injection of a corticosteroid and hyaluronic acid: a potential new approach to the treatment of trigger finger. Drugs R D. 2011;11(2):137-45*

  The aim of this study was to evaluate the feasibility and safety of ultrasound-guided injection of a corticosteroid and hyaluronic acid compared with open surgery for the treatment of trigger finger. Clinical assessment of the digital articular chain was conducted prior to treatment and after 6 weeks, and 3, 6, and 12 months. The duration of abstention from work and/or sports activity, and any treatment complications or additional treatment requirements (such as physiotherapy, compression, medication) were also recorded. The reported resultssuggest that ultrasound-guided injection of a corticosteroid and hyaluronic acid appears to be a safe and feasible approach to treat trigger finger. Even if, the open surgery remains the reference treatment, this approach is associated with a shorter recovery time, a reduced abstention from sports and, work activities.

SINOVIAL 0.8% 2ml

- *Gigante, S. Cecconi, D. Eneai, E. Cesari, G. Valerf and A. Busilacchi. Effect of subacromial injections of hyaluronan on different grades of rotator cuff lesion: a prospective study. European Journal of inflammation. 2013 Volu.11, n.3. 777-787*

  The aim of this study is to assess the safety and the effectiveness of injections of a medium-low molecular weight HA in patients with different level of rotator cuff disease. The treatment cycle consisted of three subacromial injections, each of which was separated by an interval of 15 days with SINOVIAL 0.8% (16 mg HA in 2 ml). Follow-up was at 0, 15, 30, 45 and 90 days.
  The results show that patients affected by bursitis or partial cuff tears benefit from HA, while in cuff arthropathy HA might only delay surgery or represent a palliative, on the other hand, HA was not effective in pian relief or functional recovery. VAS, Oxford- Shoulder- Score (OSS) and Constant - Murley were used for the assessment Overall, the study demonstrated the safety and the high tolerability profile of SINOVIAL, specifically for subacromial injection in shoulder.
- *Migliore A, Silvana G, Bizzi E, Massafra U, Cassol M, Michael Abilius MJ, Boni G. Use of viscosupplementation for the recovery of active football players complaining of knee pain. Open Access Journal of Sports Medicine. 2019; 10:11–15.*

The aim of this study is to assess the safety and the clinical efficacy of intra-articular hyaluronic acid administration (SINOVIAL) in active football players complaining of knee pain after sports activity. Efficacy and safety profiles of intra-articular hyaluronic acid and time needed for football players to recover and restart sports activity were examined. Lequesne index score, pain visual analog scale (VAS) score, and patient's global assessment score were recorded at time 0 (day of the first injection), 1 and 2 days after the first injection, at 2 weeks (day of the second injection), and at follow-up visits.

After one week, all parameters indicated improvement, then maintained until the end of follow-up. All patients successfully restarted playing after the first injection within 3.1±2.0 days and kept playing after the second injection (after 1 day of break). The results collected from this 6-months study confirm the safety and the effectiveness of the use of SINOVIAL in football players affected by knee osteoarthritis, with a stable improvement of symptoms and a rapid restart of sports activity.

- *Castellacci E. and Polieri T. Antalgic effect and clinical tolerability of hyaluronic acid in patients with degenerative diseases of knee cartilage: an outpatient treatment survey. Drugs Exptl. Clin. Res. 2004; 30 (2): 67-73.*

  This study is aimed to evaluate the tolerance profile and the antalgic effect of SINOVIAL weekly administered through intra-articular inject to patients with primary or secondary symptomatic knee osteoarthritis. A total of 40 outpatients were treated with a cycle of five injections of SINOVIAL, with a follow-up visit at week 7.

  No systemic adverse effects were reported and global tolerability was judged as excellent/good by almost all the patients and the investigator. In add, this treatment showed a significant clinical benefits, as demonstrated by a positive trend in Lequesne's Algo Functional Index (AFI), parallelly to a decrease into the relative scores of the pain scale, and rescue medication consumption. In conclusion, injection with SINOVIAL appeared to be safe and effective therapy for gonarthritic pain.

SINOVIAL 1.6%

- *Papalia R, Russo F, Torre G, Albo E, Grimaldi V, Papalia G, Sterzi S, Vadalà G, Bressi F, Denaro V. Hybrid hyaluronic acid versus high molecular weight hyaluronic acid for the treatment of osteoarthritis in obese patients. Journal of biological regulators and homeostatic agents, 2017, Vol. 31(N. 4 Suppl 2), 103-109*

  The aim of this clinical randomized trial was to present a comparison between two groups of 24 obese patients treated with two intraarticular injections of SINOVIAL HL (GROUP A) or two injections of high molecular weight, SINOVIAL (Group B). All patients reported a significant improvement when compared to baseline value in all outcome measures (International Knee Documentation Committee (IKDC), Knee Injury and Osteroartrhitis Outcome Score (KOOS) and Visual Analog Scale (VAS)). At 3 months follow-up, IKDC had significantly improved in patients of Group A, compared to Group B and KOOS also at 6 months. The VAS reduced significantly

more in Group A at 3 months. In conclusion, in obese patients, for which conservative treatments are recommended to avoid or at least delay the knee replacement, the viscosupplementation with HA improved function and pain of the knee.

- *A. Migliore, U. Massafral, E. Bizzii, F.Giovannangelp and S. Tormenta Intra-articular ultrasound-guided injection of Sinovial® forte 1.6% in patients affected by symptomatic hip osteoarthritis: effectiveness and safety in a large cohort of patients. European Journal of Inflammation, Vol. 10, no. 1,71-79 (2012)*

  The aim of this study was to analyse the tolerability and safety profile and the efficacy of intra-articular SINOVIAL FORTE 1.6% administered under ultrasound-guidance in patients affected by symptomatic hip osteoarthritis (OA); they were followed-up every 3 months for a total of 6 months and were offered an optional, additional injection at the 3-month follow-up visit if clinically justified. No systemic, severe or even moderate side effects were observed. Altogether, all these data confirmed the clinical effectiveness of SINOVIAL FORTE 1.6% in the treatment of patients affected by symptomatic hip OA, reducing pain and improving joint function. In parallel, the study also confirmed the tolerability and safety profile of the product. These findings make SINOVIAL FORTE 1.6% particularly suitable for patients contraindicated for NSAID use (or intolerant to) and in patients suffering from OA isolated in the hip joint.

- *Abate M, Scuccimarra T, Vanni D, Pantalone A, Salini V. Femoroacetabular impingement: is hyaluronic acid effective? Knee Surgery, Sports Traumatology, Arthroscopy 2014; 22: 889-92*

  This study has been conducted in order to report the short-term results on hip pain and function after ultrasound-guided injections of hyaluronic acid, in twenty patients suffering from mild femoroacetabular impingement were enrolled. Each patient received a 2-ml intra-articular injection of SINOVIAL at baseline and after 40 days and the same dosing after 6 months. The clinical and functional evaluation were performed at baseline and after 6 and 12 months of follow-up. Pain score, Lequesne Index, Harris Hip Score and anti-inflammatory medication consumption were recorded.

  Pain decreased after 6 and 12 months, Lequesne Index was reduced, and the mean Harris Hip Score improved before treatment to 12 months. Overall, Hyaluronic acid injection may provide good early results, improving hip function and reducing impairment in daily activities. Local side effects after injection were observed only in 2 cases. In conclusions, Hyaluronic acid is safe and effective in the treatment of mild femoroacetabular impingement.

- *Carulli C, Rizzo AR, Innocenti M, Civinini R, Castaman G, Innocenti M. Viscosupplementation in symptomatic haemophilic arthropathy of the knee and ankle: experience with a high molecular weight hyaluronic acid. Haemophilia, 2020; 26(4): e198-e200*

  The aim of the present communication was the critical analysis of the clinical effects of viscosupplementation by HMWHA in terms of pain relief, functional improvement, and bleeding rate in a population of naïve patients (thirteen subjects) with haemophilia affected by haemophilic arthropathy at a haemophilia centre, with a decade of very positive experience of LMWHA treatment. No side effects were recorded after the injections. Median e Haemophilia Joint Health score, Numeric Rating scale and annual bleeding rate improved with a statistical

significance; median range of movement evaluation showed slight improvements but was not statistically significant.

SINOVIAL 2%

- *Abate M, Vanni D, Pantalone A, Salini V. Hyaluronic acid in knee osteoarthritis: preliminary results using a four months administration schedule. International Journal of Rheumatic Diseases 2015*

  This study was devoted to evaluating the therapeutic trajectory of intra-articular injections of hyaluronic acid in patients with knee osteoarthritis. They received, after a weekly injection of SINOVIAL FORTE (32 mg/2 mL of HA) for 3 weeks, a single injection of SINOVAL ONE (50 mg/2.5 mL hyaluronic acid) at 4-month interval (4, 8 and 12 months).
  Clinical assessment (visual analogic scale for pain at rest and during activities, Lequesne Index, Knee Injury and Osteoarthritis Outcome Score, and monthly non-steroidal anti-inflammatory drug consumption) was performed at baseline, and after 1, 4, 6, 8, 12 and 14 months.
  In conclusion, a single HA injection treatment schedule every 4 months allows positive results in terms of reduced pain and improved function, optimizing the protective properties of the hyaluronic acid used.
- *Polacco A, Beomonte Zobel B, Polacco M, Scarlata S, Gasparro F, Del Vescovo R, Scarciolla L. The effect of intra-articular hyaluronic acid (sinovial® one) on knee osteoarthritis: a preliminary study. European Journal Of Inflammation. Vol. 11, no. 3, 0-0 (2013)*

  The aim of this study was to assess the safety, the efficacy and the duration of the effects of a single intra-articular injection of SINOVIAL ONE, on patients with knee arthritis. The double-blind study enrolled 21 patients (24 knees) with symptomatic knee osteoarthritis, classified into moderate, severe and very severe osteoarthritis using WOMAC pain functional Index and the Kellgren and Lawrence scales.
  After four months, there was improvement in measured clinical parameters in 77.6% of the 24 treated knees, particularly in patients with moderate and severe osteoarthritis. No local or systemic adverse events were observed. These results suggested that SINOVIAL ONE was safe and effective for patients with knee osteoarthritis, providing long-lasting improvement in clinical parameters.
- *La Paglia E, Barbero S, Belletti M, Boccuzzi F, Di Caterino F, Faletti C, Mazzucco L, Schiraldi M, Valentini D, Zawaideh JP. Femoro-acetabular impingement syndrome in young patients: US-guided treatment with platelet rich plasma in association with hybrid form of hyaluronic acid in comparison with hyaluronic acid group control. Giornale Italiano di Ortopedia e Traumatologia 2017; 43: 215-226.*

  The aim of this study was to evaluate retrospective the results of a combined intra-articular therapy with Platelet-Rich Plasma in association with hybrid form hyaluronic acid (SINOVIAL HL) and high molecular weight hyaluronic acid (SINOVIAL) in young patients with femoro-acetabular impingement syndrome. 16 patients were treated with intra-articular injection of PRP + SINOVIAL HL and compared the results with a 16-patient control group treated with intra-

articular injection of H-HA (SINOVIAL). MRI and clinical and functional evaluation (with HOOS) were assessed at baseline and 2 and 6 months after treatment.
The results of this study demonstrate that combined SINOVIAL HL + PRP intra-articular injection in hip arthropathy in FAI syndrome is effective, getting early and lasting clinical improvement in a group of young patients with low-grade condropathy.

5.4. An overall summary of the clinical performance and safety

Intra articular injection of hyaluronic acid is a treatment method widely used in the orthopaedic field for viscosupplementation. SINOVIAL is an intrarticular device, available in three different concentrations 0,8%, 1,6%, 2%, intended to be used in case of pain or reduced mobility due to degenerative diseases and post traumatic diseases of the large joints. Furthermore, SINOVIAL 0,8% is also intended for the treatment of pain or reduced mobility in degenerative diseases post traumatic conditions or changes in the joint and tendons of large and small joints. The key functional ingredient is Hyaluronic acid, an integral substance of synovial fluid, that acts as joint lubricant during shear stress and as shock absorber during compressive stress. In tendons, it promotes the tendon gliding, reducing tendon adhesions.
Several studies have been conducted with each variant of the device, in order to support the claims, the beneficial effects and the safety profile. Overall, the results of the studies reported in the paragraphs above, confirm for each concentration of SINOVIAL, the effectiveness in reducing pain and restoring joint mobility in case of degenerative diseases (e.g. osteoarthritis) and post traumatic conditions and its safety profile. Based on the data retrieved and discussed above, SINOVIAL resulted to be effective in improving symptoms in large joints also in obese patients, by reducing pain (VAS score) and improving clinical outcomes related to joint function and mobility, with a rapid and prolonged effect, and allowing a significant reduction in the weekly consumption of paracetamol or NSAIDs. Several other evidences support the efficacy of the SINOVIAL 0.8% for the treatment of small joints disorders, improving pain levels, chewing efficacy, functional limitation, subjective perceived efficacy, and functionality of the tendon sheath in tendinopathies.
No clinical data from literature has been retrieved describing severe, life threating adverse events, related to the use of SINOVIAL. Few and mild /moderate adverse events occurred after the use of the product as specified in the leaflet, and in general were transient and disappeared in few days. All contraindications and precautions are reported in the leaflet in order to avoid occurrence of serious adverse events. All risks related to the use of the product have been considered by the Manufacturer, and it is possible to state that benefits deriving from the use of the product outweigh the risks.
Overall, based on the results obtained from the clinical studies performed, data from literature and derived from the consolidated use of these devices, it can be concluded that SINOVIAL (0.8%, 16%, 2%) is effective in reducing pain and improving mobility due to degenerative diseases (arthritis), post-traumatic conditions and alterations of the large and small joints and tendons (e.g., acute and chronic tendinopathies).

5.5. Ongoing or planned post-market clinical follow-up

During the Post Market Clinical Follow up activities, the Manufacturer will collect additional clinical data thorough a survey with questionnaires, that will be submitted to the professional users in order to analyse and verify their experience after the use of the device. The survey aims to collect efficacy data, in relation to the clinical performance endpoints provided for the product, defined in coherence with the anatomical areas of interest and with the treatment plan (n. cycles), in relation to the indications of the product. Questions aimed to collect and monitor the safety of the device through the incidence of expected adverse events, and to confirm the absence of events not yet identified.

6. Possible diagnostic or therapeutic alternatives

Osteoarthritis

Osteoarthritis (OA) is a progressive, degenerative disease of the synovial joints causing joint pain and functional impairment with different degrees of disease severity that requires long-term management with various treatment options over the course of the disease.

Several guidelines for the management of OA are available developed by clinical experts such as, for example, the *European Society For Clinical And Economic Aspects Of Osteoporosis, Osteoarthritis And Musculoskeletal Diseases (ESCEO),* the *American College of Rheumatology (ACR) e the Osteoarthritis Research Society International (OARSI),* the *European Alliance of Associations for Rheumatology (EULAR),* the *Arthroscopy Association of Canada (AAC).* The most used pharmacological and non-pharmacological agents are proposed with different strengths of recommendations across the different societies' guidelines. In general, the guidelines for the management of OA suggest that patients should be educated regarding nonpharmacological interventions including lifestyle, weight loss (for those who are overweight), and exercises that do not involve high-impact activities especially in patients with mild to moderate OA. However, there are not clearly defined parameters for the nature, frequency and duration and physical therapies programs to assign for patients with OA.

Currently no pharmacologic interventions exist that can decrease the progression of the disease or reverse existing damage. Pharmacological treatments are usually started when the OA becomes symptomatic since pain is the main cause of reduced everyday activities. The wide range of available agents includes oral, topical and intra-articular treatments able to provide an improvement in the patient's quality of life, either alone or more often combined with other non-surgical approaches.

Oral interventions include Acetaminophen, Nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics and Slow Acting Drugs for OA (SYSADOAs). Of note, when these treatments are prescribed, it is important to consider the patients status, comorbidities and treatments related side effects. It is recommended to avoid the use of acetaminophen and NSAIDs for a long time since they could lead liver damage, or other adverse events, such as stomach irritation, nausea, vomiting and dizziness etc. Similarly, since the potential abuse could be associated with important gastrointestinal and cognitive adverse events, opioids like tramadol should be an option only for patients who have not responded to acetaminophen or NSAID therapy or cannot tolerate them because of adverse effects.

Another important pharmacological treatment option for osteoarthritis is represented by the Slow Acting Drugs for OA (SYSADOA), that includes oral glucosamine sulphate and related compounds, such as chondroitin sulphate. In particular, chondroitin sulphate (CS) is a glycosaminoglycan, an important structural constituent of the extra-cellular matrix of the cartilage, which contribute to give the cartilage its mechanical and elastic properties. Therefore, the administration of exogenous CS contributes to the maintenance of the articular cartilage, thus limiting the erosive action of the disease. CS has proven to be a valuable therapeutic tool for the symptomatic treatment of OA, but it has also structure modifying properties acting on cartilage structure (SMOAD). There are some differences among the International Recommendations regarding the use of SYSADOAs, however, recent meta-analyses indicate the potential benefits related to their use in patients with knee OA. In fact, it has been shown that prescription-grade CS is more effective in reducing pain in knee OA than nutraceutical grade or over-the-counter (OTC) chondroitin preparations. Additionally, the safety profile of prescription-grade CS is good and the use of pharmaceutical-grade CS it is also recommend by the ESCEO guidelines, as first-line long-term therapy in symptomatic knee OA as both single therapy and in combination with acetaminophen.

Topical NSAIDs (i.e diclofenac) offer a favourable risk benefit profile and may be safely used in combination with other treatment strategies for optimal management of OA.

Nowadays, among the non-surgical strategies, intra-articular therapies are commonly use for the reduction of the symptoms of this disease. One of them, consists in the intra-articular administration of corticosteroids, that are used to treat osteoarthritis patients affected by moderate-severe joint pain who are not responding to oral anti-inflammatory or analgesic drugs. Injection of corticosteroids alleviate pain for few weeks but the number of injections each year is generally limited, because the medication can worsen joint damage over time and can cause other side effects.

Platelet-Rich Plasma (PRP) is another injectable option of treatment, that provides a concentrate of autologous growth factors that can be used to enhance tissue regeneration, and lead to reduce inflammatory distress. Side effects are uncommon, but the biological effects depend on differences between some of the key characteristics, including platelet concentration, anticoagulant and coagulation activation agent type, presence of inflammatory white blood cells, and activation level.

However, among the intra-articular treatment, hyaluronic acid injection is the most commonly non-surgical therapy used for OA. After several decades of use, it is usually recognised as a safe treatment for OA, restoring the viscoelastic behaviour of synovial fluid in terms of joint lubrication, shock absorption, and reducing mechanical stress on the joint. Viscosupplementation acts by replacing or reinforcing the rheological and protective properties of the synovial fluid, decreasing pain and improving joint functionality. The most commonly adverse events reported due to the use of intra-articular injection of HA are mild, transient local reactions such as pian, inflammation, swelling and pain at the injection site is rare and short-lived.

In severe case of the OA disease, the arthroplasty is performed to replace the damage surface of the bones with prostheses. This approach is considered for the later stage, restricted to patients with more severely affected functional status since risks of serious medical and post-surgical complications often occurred and this option of treatment is not often suitable for all patients and all joints.

Tendinopathies

Tendon damage can be acute or chronic, and caused by intrinsic or extrinsic factors, alone or in combination. Chronic tendinopathies represent a major problem in the clinical practice of sports orthopaedic surgeons, sports doctors and other health professionals involved in the treatment of athletes and patients that perform repetitive actions. No gold standard for the management of tendinopathies is documented, since there are different controversial results, and treatments have been based on doctors' experience and usual treatment approach.

Conservative management of tendinopathies includes several options such as rest, anti-inflammatory medication, injection therapies, physiotherapy and eccentric exercise, even if the benefits of this latter therapy is uncertain. In the initial acute phase of tendinopathy, rest and immobilisation may be considered to try and control exacerbating factors, but then specific exercises are necessary, in order to avoid immobilisation. Peritendinous injections of hyaluronic acid (HA) also seem to be an effective experimental therapeutic option, when physical treatment regimens are failed, for the management of chronic tendinopathy. HA induced improvement of viscoelastic properties allows a reduction in the surface friction of tendons and increases their gliding ability. In case of pain and swelling, pharmacological treatments, such as NSAIDS and corticosteroids, are commonly use (oral, topical and injected interventions) to modulate the symptoms, used as a standard management option. However, potential harms and adverse events are commonly reported.

Even this technique is not definitely proven, PRP is also used to promote the tendon healing since stimulates soft tissue healing thanks to the high content of cytokines and cells which increase the expression of collagen and vascular endothelial factors.

Finally, surgery is the preferred treatments in later stages of tendinopathies even a best surgical treatment option still does not exist. The surgical intervention aims to excise fibrotic adhesion, remove areas of failed healing and make multiple longitudinal incisions in the tendon detect intra-tendinous lesions and to restore vascularity.

In this context, IBSA Farmaceutici Italia srl has developed SINOVIAL in different presentations (0.8%, 1.6% and 2.0%), intended for the treatment for pain or reduced mobility due to degenerative diseases and post-traumatic diseases of the joints. SINOVIAL 0.8% is also used in tendinopathies, and according to its lubricating and viscoelastic characteristics, acts at the level of the tendon sheath, improving the sliding of the tendon and the physiological processes of healing, repair, thus preventing the formation of post-surgery adhesions.

7. *Suggested profile and training for users*

IBSA Institut Biochimique SA, the Head Quarter of IBSA Farmaceutici Italia srl, manufacturer of SINOVIAL, organizes regularly educational courses and training sessions dedicated to IBSA Affiliates/Distributors and to physicians of different countries. These courses are aimed at training them on the correct infiltration practice and on the use of the ultrasound (US) technique that is propaedeutic to the utilization of i.a. devices.

8. Reference to any harmonised standards and CS applied

HARMONISED STANDARD	
• EN ISO 10993-9:2021	Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products (ISO 10993-9:2009)
• EN ISO 10993-12:2021	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (ISO 10993-12:2012)
• EN ISO 11737-1:2018/A1:2021	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products (ISO 11737-1:2018)
• EN ISO 13485:2016	Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2016)
• EN ISO 15223-1:2021	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements (ISO 15223-1:2016, Corrected version 2017-03)

NON HARMONISED STANDARD	
Use of following non harmonised standard is necessary to comply with relevant GSPR because, for the time being, in absence of harmonized standards, they represent the state of the art to meet the relevant requirement.	
• EN 285:2015+A1:2021	Sterilization - Steam sterilizers - Large sterilizers
• IEC 62366-1:2015+AMD1:2020	Medical devices Application of usability engineering to medical devices
• IEC/TR 62366-2:2016	Medical devices Guidance on the application of usability engineering to medical devices
• EN ISO 10993-1:2020	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2018, including corrected version 2018-11)
• EN ISO 10993-2:2006	Biological evaluation of medical devices - Part 2: Animal welfare requirements (ISO 10993-2:2006)

• EN ISO 10993-3:2014	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993-3:2014)
• EN ISO 10993-5:2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009)
• EN ISO 10993-6:2016	Biological evaluation of medical devices - Part 6: Tests for local effects after implantation (ISO 10993-6:2016)
• EN ISO 10993-10:2013	Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization (ISO 10993-10:2010)
• EN ISO 10993-11:2018	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO 10993-11:2017)
• EN ISO 10993-17:2009	Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances (ISO 10993-17:2002)
• EN ISO 10993-18:2020	Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process (ISO 10993-18:2020)
• EN ISO 14155:2020	Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020)
• EN ISO 14971:2019+A11:2021	Medical devices - Application of risk management to medical devices (ISO 14971:2019)
• EN ISO 17665-1:2006	Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 17665-1:2006)
• EN ISO 11138-1:2017	Sterilization of health care products - Biological indicators - Part 1: General requirements (ISO 11138-1:2017)
• EN ISO 11138-3:2017	Sterilization of health care products - Biological indicators - Part 3: Biological indicators for moist heat sterilization processes (ISO 11138-3:2017)
• EN ISO 11138-4:2017	Sterilization of health care products - Biological indicators - Part 4: Biological indicators for dry heat sterilization processes (ISO 11138-4:2017)

• EN ISO 11737-2:2020	Sterilization of health care products - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process (ISO 11737-2:2019)
• EN ISO 11607-1:2020	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019)
• EN ISO 11607-2:2020	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019)
• EN ISO 14644-1:2015	Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration (ISO 14644-1:2015)
• EN ISO 14644-2:2015	Cleanrooms and associated controlled environments - Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration (ISO 14644-2:2015)
• EN ISO 14644-3:2019	Cleanrooms and associated controlled environments - Part 3: Test methods (ISO 14644-3:2019)
• EN ISO 7886-1:2018	Sterile hypodermic syringes for single use Syringes for manual use
• ISO 11040-4:2015	Prefilled syringes Glass barrels for injectables and sterilized subassembled syringes ready for filling
• ISO 11040-5:2012	Prefilled syringes Plunger stoppers for injectables
• ISO 11040-7:2015	Prefilled syringes Packaging systems for sterilized subassembled syringes ready for filling
• ISO 11040-8:2016	Prefilled syringes Requirements and test methods for finished prefilled syringes
• ISO 8871-4:2006	Elastomeric parts for parenterals and for devices for pharmaceutical use Biological requirements and test methods
• EN 556-1:2001	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices
• EN ISO 14630:2012	Non-active surgical implants - General requirements (ISO 14630:2012)

• ISO 2859-1:1999	Sampling procedures for inspection by attributes Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection

MDCG	
• MDCG 2021-11	Guidance in Implant card – Device types
• MDCG 2019-8 v2	Guidance document implant card on the application of Article 18 Regulation (EU) 2017/745 on medical device
• MDCG 2021-19	Guidance note integration of the UDI within an organisation's quality management system
• MDCG 2018-1	Guidance on basic UDI-DI and changes to UDI-DI
• MDCG 2019-1	MDCG guiding principles for issuing entities rules on basic UDI-DI
• MDCG 2019-2	Guidance on application of UDI rules to device-part of products referred to in art. 1(8), 1(9) and 1(10) of Regulation 745/2017
• MDCG 2018-4	Definitions/descriptions and formats of the UDI core elements for systems or procedure packs
• MDCG 2018-3	Guidance on UDI for systems and procedure packs
• MDCG 2019-9	Summary of safety and clinical performance
• MDCG 2020-6	Guidance on sufficient clinical evidence for legacy devices
• MDCG 2020-7	Guidance on PMCF plan template
• MDCG 2020-8	Guidance on PMCF evaluation report template
• MDCG 2020-10/2 • MDCG 2020-10/1	Guidance on safety reporting in clinical investigations Appendix: Clinical investigation summary safety report form
• MDCG 2020-13	Clinical evaluation assessment report template
• MDCG 2020-5	Guidance on clinical evaluation – equivalence
• MDCG 2021-8	Clinical investigation application/notification documents

9. Revision history

Revision	Validated by the NB	Date	Description of main changes	Languages
Rev. 0	Not yet/ongoing	02/2022	First issue of SSCP according to the Technical File.	English (Validated by the NB)
Rev. 1	Validated	04/2022	Revision due to the Non Conformity	English (Validated by the NB)