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

"HILOW VISCO-SUPPLETIVE JOINT DEVICE"

3.2%- 16 mg (H-HA) + 16 mg (L-HA)/1 ml
3.2%- 32 mg (H-HA) + 32 mg (L-HA)/2 ml
4.5%- 45 mg (H-HA) + 45 mg (L-HA)/2 ml

With the following brand names:
HILOW
SINOVIAL HL
INTRAGEL HL

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****.*

SUMMARY

1. *Device identification and general information*

1.1. Device trade name(s)

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

- 3.2%- 16 mg (H-HA) + 16 mg (L-HA)/1 ml
- 3.2%- 32 mg (H-HA) + 32 mg (L-HA)/2 ml
- 4.5%- 45 mg (H-HA) + 45 mg (L-HA)/2 ml

Can be marketed with the following brand names:

- HILOW
- SINOVIAL HL
- INTRAGEL HL

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 803363895IA0014R
- for the kit is 803363895IAK00167

The basic UDI, for the medical devices covered by this technical file is 803363895IA0014R.

1.5. Medical device nomenclature description / text

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

1.6. Class of device

"HILOW 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 2014. At the Date of Application (DoA) of the MDR, 26th May 2021, the Medical Device "HILOW VISCO-SUPPLETIVE JOINT DEVICE" was covered by the following certificates:

- EC design-examination certificate n. EPG-0096-18, dated 24.04.2018
- 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 "HILOW 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

Eurofins 0477

2. Intended use of the device

2.1. Intended purpose

"HILOW VISCO-SUPPLETIVE JOINT DEVICE" with its particular formula belongs to the latest generation of intra-articular treatments. "HILOW 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. "HILOW VISCO-SUPPLETIVE JOINT DEVICE" reduces pain in the joint and encourages recovery of the associated joint mobility. Clinical data have demonstrated that "HILOW VISCO-SUPPLETIVE JOINT DEVICE" 3.2%, in combination with the laser therapy, can improve the symptomatology correlated to the tendinopathy.

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

"HILOW VISCO-SUPPLETIVE JOINT DEVICE" is indicated in case of pain or reduced mobility due to degenerative affections (e.g. arthrosis), post-traumatic disorders associated with acute and chronic articular disability in the large and "HILOW VISCO-SUPPLETIVE JOINT DEVICE" 3.2% in small joints.

"HILOW 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

CONTRAINDICATIONS
"HILOW VISCO-SUPPLETIVE JOINT DEVICE" should not be injected in the presence of an infected or severely inflamed joint or if the patient has a skin affection or infection in the injection site area.

3. Device description

3.1. Description of the device

The device "HILOW VISCO-SUPPLETIVE JOINT DEVICE" consists of a pre-filled syringe, containing a buffered saline solution of hyaluronic acid with viscoelastic properties. This medical device contains 3.2% or 4.5% of highly purified sodium hyaluronate with two different molecular weights. The other components of the product are sodium chloride, sodium phosphate and water for injections. The High Molecular Weight Hyaluronic Acid chains (H-HA) and Low Molecular Weight Hyaluronic Acid chains (L-HA) contained in "HILOW VISCO-SUPPLETIVE JOINT DEVICE", thanks to a specific and patented treatment of the solution (NAHYCO® Hybrid Technology), interact with each other providing unique rheological characteristics to the device thus allowing the administration of higher concentrations of hyaluronic acid without increasing the viscosity. The device "HILOW VISCO-SUPPLETIVE JOINT DEVICE" is provided in 1.25ml, 2.25ml glass syringes containing respectively 1ml, 2ml of product. It is for a single use only and the content of the syringe is sterile and pyrogen-free. The injection may only be administered by a medical practitioner.

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 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:

- HILOW – SINOVIAL HL – INTRAGEL HL – 3,2% - 16 mg (H-HA) + 16 mg (L-HA)/1 ml Hyaluronic Acid Sodium Salt with two needle
  - 1 ago 22 G x 1 ½" (0,7 x 40 mm);
  - 1 ago 29 G x ½" TW (0,3 x 12 mm);

- HILOW – SINOVIAL HL – INTRAGEL HL – 3,2% - 32 mg (H-HA) + 32 mg (L-HA)/2 ml Hyaluronic Acid Sodium Salt with needle 21 G x 1 ½" (CE0197; Manufacturer TERUMO Europe N.V).
- HILOW – SINOVIAL HL – INTRAGEL HL – 4.5% - 45 mg(H-HA) + 45 mg (L-HA)/2 ml Hyaluronic Acid Sodium Salt with needle 21 G x 1 ½" (CE0197; Manufacturer TERUMO Europe N.V).

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

The device is not intended to be used with any other accessories except for needles that are included in the product's box.

4. Risks and warnings

4.1. Residual risks and undesirable effects

According to Risk Assessment, it is possible to state that Residual Risks are intrinsic and cannot be further reduced and that the Overall Residual Risk can be considered as acceptable. For these reasons, "HI-LOW 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 "HI-LOW VISCO-SUPPLETIVE JOINT DEVICE" may cause undesirable effects locally. During the use of "HI-LOW 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 undesired effects which occur after the treatment.
In case of incident, inform the Manufacturer or the Competent Authority.

Post-market experience of the cumulative period, September 2015 -the date of the launch of the product- to December 2020 showed a very low incidence (0,008%) of adverse events (AEs) taking into account the cumulative patient exposure (a total of 95.142 exposed patients): 5 cases (2 incidents) describing a total of 8 AEs have been collected by IBSA.
The only adverse events that can be attributed (or only in part) to the product (i.e. adverse reactions) are injection site reactions (ISRs) i.e., 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 ice cold 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:
"HI-LOW 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 and needles are packed in a sealed blister pack.
- The outer surface of the syringe is not sterile.
- Do not use "HILOW VISCO-SUPPLETIVE JOINT DEVICE" after the expiry date indicated on the package.
- Do not use "HILOW 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 "HILOW 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, "HILOW VISCO-SUPPLETIVE JOINT DEVICE" must immediately be used and discarded after use.
- "HILOW VISCO-SUPPLETIVE JOINT DEVICE" is indicated for adult patients.
- Keep out of the reach and sight of children.
- 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.
- Do not use "HILOW VISCO-SUPPLETIVE JOINT DEVICE"® in case of known hypersensitivity or allergies to the components 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 conducted.

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 HL 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 HL. 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 study has been performed on the SINOVIAL HL (3,2 %) still marketed under the Directive 93/42/EEC.

Migliore A. et al. Knee Osteoarthritis Pain Management with an Innovative High and Low Molecular Weight Hyaluronic Acid Formulation (HA-HL): A Randomized Clinical Trial. Rheumatol Ther. 2021 Dec;8(4):1617-1636.

Reference to the clinical trial /database	NCT03200288
Countries (if extra EU) where the study was conducted	The study was conducted in 31 centres in 5 European countries (1 in Belgium, 4 in Germany, 6 in Hungary, 3 in Italy and 17 in Poland).
Intended use of the Medical device used in the investigation	The device was used in symptomatic treatment of pain in patients with knee osteoarthritis (OA)
Study design	Multi-centre, double-blind, placebo-controlled, randomized, parallel-group study
Endpoints	Primary objective The primary objective of the study was the change from screening to week 24of Visual Analogue Scale (VAS) pain score (calculated as a VAS measure ranging from 0 - no pain - to 100 mm – unbearable pain) in moderate-to-severe symptomatic knee osteoarthritis.

	Secondary objectives Secondary outcomes included Lequesne's algo-functional index, EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), Outcome Measures in Arthritis Clinical Trials Osteoarthritis Research Society International (OMERACT-OARSI) response and rescue medication usage. Safety: The safety variables of the study included the incidence and the frequency of adverse events; Change from baseline in vital signs and in physical examination parameters. Level of treatment satisfaction was assessed by patient at baseline (times: within 15 minutes after the intra-articular injection, 24 hours after the injection, at week 1 and week 6).
Inclusion and exclusion criteria	Inclusion criteria: • Female and male subjects ≥ 40 to 80 years of age; • Patients with primary knee OA according to American College of Rheumatology (ACR) criteria; • Patients with Kellgren & Lawrence grade 2–3 radiographic evidence of OA; • Patients with symptoms of at least 3 months in duration; • Patients with moderate-to-severe pain at inclusion • Screening pain intensity in the target knee measured by 100 mm Visual Analogue Scale (VAS) was required to be C 40 mm VAS (and B 20 mm in the contralateral knee) and confirmed at randomization after wash-out from analgesics/NSAIDs. Participants had to be willing and able to comply with study procedures, including usage of paracetamol (acetaminophen) as the only analgesic. Exclusion criteria: Exclusion criteria included conditions or medications that could have confounded the protocol assessments and conditions that could have been adversely affected by an intra-articular injection. • Secondary (post-traumatic) knee OA of the target and non-target joints • Kellgren and Lawrence radiological grade 4 knee OA • Knee joint replacement/arthroplasty of the target knee or arthroscopy, osteotomy, or surgery of the target knee in the past 12 months • Significant injury to the target knee in the last 6 months • Body mass index (BMI) C 32 kg/m2 • Any musculoskeletal condition affecting the target knee that would impair proper clinical assessment • Symptomatic hip OA or other health condition interfering with adequate study endpoints evaluation • Significant venous or lymphatic stasis • Systemic (oral or parenteral) or topical corticosteroids at the target knee in the past 3 months or intra-articular corticosteroid treatment of the target knee in the past 3 months or the non-target knee or other joints in the past 4 weeks

	• Topical anti-inflammatories and analgesics applied at the target knee in the past 48 h • Viscosupplementation with HA or joint-lavage in the target knee in the past year • Symptomatic slow-acting drugs for OA (SYSADOA) • Chronic or recurrent use of narcotics, analgesics or • NSAIDs or recent use of analgesics other than paracetamol and NSAIDs • Recently initiated treatment with drugs having an influence on pain • Anticoagulant therapy • Infection, skin diseases, other disease, or trauma in the area of the injection site or joint • Allergy or hypersensitivity to hyaluronic acid or paracetamol • Major surgery scheduled in the next 6 months • Participation in another clinical trial within the preceding 3 months • Pregnant or breast-feeding women or lack of adequate contraception
Number of enrolled patients	692 subjects were randomly assigned to the two treatment groups (347 to HL-01 and 345 to placebo), and 16 patients out of the 708 screened were not randomized to either group.
Study population	Overall, 663 patients completed the study and 29 discontinued prior to the final visit at 24 weeks, with discontinuations being slightly more prevalent in the placebo group (because of voluntary withdrawal or loss of follow-up).
Summary of the study methods	The study included a screening/wash-out period for analgesics and non-steroidal anti-inflammatory drugs(. The administration of the investigational medical device at baseline was followed by further 5 visits for a total of 24 weeks of follow-up. The HL-01 formulation contained 32 mg of high and 32 mg of low molecular weight, non-chemically modified, HA sodium salt per 2 mL of 3.2% buffered solution. HL-01 was administered as a single intra-articular injection at Day 1. Only one knee was treated and evaluated during the study, if a bilateral knee OA was present, only the most symptomatic one, complying with the inclusion/exclusion criteria, was treated.
Summary of results	This study showed that a single injection of SINOVIAL HL is more effective than placebo in treating pain associated with knee OA, with the salutary effects beginning at one-week post-administration and continuing through week 24,. Similarly, for all secondary outcome variables, the results showed that both treatments were equally well-tolerated given the incidence of adverse events, irrespective of classification, were indistinguishable.

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

The following studies have been conducted on the product SINOVIAL HL (3.2%) still marketed under the Directive 93/42/EEC. For all these studies, a brief summary is reported below.

- *Tenti S. et al. Can hybrid hyaluronic acid represent a valid approach to treat rizoarthrosis? A retrospective comparative study. BMC Musculoskeletal Disorders 2017; 18: 444.*
  The aim of this 6-months observational comparative study was the assessment of the efficacy and tolerability of intra-articular injections of SINOVIAL HL in comparison to triamcinolone in patients with trapeziometacarpal joint (TMJ OA). The medical records of 100 patients with monolateral or bilateral TMJ OA treated with two injections of SINOVIAL HL or of triamcinolone acetonide have been retrospectively analysed with a clinical assessments after the first and the second injection and after 1, 3 and 6 months. The results suggested that the SINOVIAL HL may be more effective than triamcinolone in pain relief and joint function improvement with a rapid and persistent effect: both therapies provided effective pain relief and joint function improvement, but the benefits achieved were statistically significantly superior in the SINOVIAL HL Group. SINOVIAL HL was associated with a significant decrease in the duration of morning stiffness and with a significant improvement in the HAQ score and physical component summary (PCS)-SF-36. Lastly, the hybrid formulation seems to be a better and safe alternative treatment in comparison with triamcinolone for the management of this frequent condition
- *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, 31(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). Patients were followed-up through to 6 months. 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.
  The treatment with SINOVIAL HL resulted to be more effective on pain reduction and function improvement compared to SINOVIAL especially at mid-term follow-up.
- *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 purpose of this study was to evaluate the results of a combined intra-articular therapy with Platelet-Rich Plasma (PRP) in association with hybrid form hyaluronic acid SINOVIAL

HL and high weight hyaluronic acid (H-HA) intra-articular injection (SINOVIAL) in two cohorts of young patients with femoro-acetabular impingement (FAI) syndrome. 16 patients have been treated with intra-articular injection of PRP + SINOVIAL HL and compared the results with 16 patients control group treated with intra-articular injection of H-HA (SINOVIAL). The results of this retrospective 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 younger patients affect by low degree condropathy.

- *Papalia R. et al. Comparing hybrid hyaluronic acid with PRP in end career athletes with degenerative cartilage lesions of the knee. Journal of biological regulators and homeostatic agents, 2016, 30(4 Suppl 1), 17-23*

  This randomized controlled trial aims to investigate the effect of SINOVIAL HL compared to PRP for the treatment of cartilage lesions among athletes at the end of their career. 48 professional soccer players were randomized into two groups: 24 patients received 3 injections of SINOVIAL HL and 23 patients received 3 intra-articular injections of PRP. All patients achieved a statistically significant clinical improvement from preoperative to postoperative time in both groups but the SINOVIAL HL group showed a significant superiority compared to PRP group at 3 and 6 months. Intergroup differences decrease gradually until loss of significance at 12 months follow-up.
- *R Papalia, B Zampogna, F Russo, G Torre, S De Salvatore, C Nobile, MC Tirindelli, A Grasso, G Vadala, V Denaro. The combined use of platelet rich plasma and hyaluronic acid: prospective results for the treatment of knee osteoarthritis Journal of biological regulators and homeostatic agents, 2019, 33(1), 21-28*

  The aim of this study is to evaluate the effect of combined autologous PRP and SINOVIAL HL) viscosupplementation on clinical outcomes of patients with knee OA, by assessing the subjects before and after injective treatment. The study was conducted on 60 patients with an age between 40 and 70 years old affected by unilateral symptomatic knee osteoarthritis (stage II and III of Kellgren-Lawrence scale) nonresponsive to pharmacologic and rehab treatment, divided in two groups, the group A with injection of SINOVIAL HL and group B with SINOVIAL HL +PRP. Each patient received 3 injections at an interval of 1 week for 3 consecutive weeks. The patients were evaluated by KOOS and VAS at 3, 6 and 12 months after treatment. The results showed a significantly better result for the group B concerning the KOOS value, at 3 months and at 6 months but this difference, although clinically relevant, lost the statistical significance at 12 months. The VAS trend differently showed a significant difference at 3 and 12 months, while at 6 months the superiority of group B did not achieve statistical significance. Therefore, it is possible to state from the results obtained that combined PRP and HHA treatment is a safe and efficacious procedure and better than HHA injective therapy alone.
- *E. Bartoloni, F. Luccioli, G. La Paglia, G. Cafaro, E. Marcucci, R. Gerli. Effect of Sinovial High-Low® injections in trapeziometacarpal osteoarthritis CliniCal and ExpErimEntal rhEumatology 2018*

The aim of this prospective pilot study was to prospectively assess the effect of Sinovial HL injections in terms of pain relief and articular function in Trapeziometacarpal joint OA. Twelve patients received one cycle of two ultrasound-guided injections (baseline and 15 days apart) of 1 ml of SINOVIAL HL. Pain on VAS scale and DASH questionnaire were recorded at baseline and at 1 , 3 and 6 months. A statistically significant reduction of pain was observed after 3 and 6 months, but not after 1 month, in comparison to baseline. Disability of the Arm, Shoulder and Hand score significantly improved at each time points, in comparison to baseline. No side effects were reported. Therefore, the local administration of SINOVIAL HL resulted to be effective in reducing pain and improving hand function in patients with symptomatic thumb OA.

- *Manciameli A. and Peruzzi M. Treating moderate gonarthrosis with intra-articular injections of sodium salt hyaluronic acid. Giornale Italiano di Ortopedia e Traumatologia 2018; 44: 146-149*

  The aim of these clinical cases was to demonstrate that intra-articular injections of hyaluronic acid in a knee with arthrosis reduce pain and improve the function of the joint. The benefits of this treatment with hyaluronic acid are consistent in terms of pain reduction, an increase in the patient's overall quality of life, and are long lasting with good outcomes also over 6 months from the injections cycle. The infiltration of hyaluronic acid is also a safe procedure, as major or minor complications can occur only in a very low percentage of cases.
- *Abate M. and Salini V. Efficacy and safety study on a new compound associating low and high molecular weight hyaluronic acid in the treatment of hip osteoarthritis. International Journal of Immunopathology and Pharmacology, 2017*

  The aim of this paper was to report the efficacy and safety profile of SINOVIAL HL in patients suffering from moderate-severe hip OA. The results have been compared with those obtained retrospectively from a cohort of patients treated with high molecular weight HA. Twenty patients with moderate-severe hip OA were enrolled, treated with an intra-articular ultrasound-guided injection of SINOVIAL HL at baseline and after 40 days. Clinical and functional evaluation (VAS for pain, Lequesne Index, Harris Hip Score) were assessed at baseline and repeated at three and six months. The data collected were retrospectively compared with those obtained in a cohort of 20 patients, treated with high molecular weight hyaluronic acid.

  The intra-group comparison showed a significant improvement in clinical and functional outcomes at three and six months in both cohorts, while the infra-group comparison showed better results in the patients treated with the study compound at six months. The results demonstrated that a SINOVIAL HL is effective and safe in the management of patients suffering from hip OA and provides better therapeutic results in comparison to high molecular weight HA.
- *Conforti M. Combination of laser needling and hyaluronic acid infiltration treatments for rotator cuff calcific tendinopathies. Gazz Med Ital - Arch Sci Med 2020;179:665-74.*

This study investigated the antalgic efficacy of a combination of SINOVIAL HL injection followed by low-thermal impact multi-frequency intra-articular laser therapy, in the treatment of calcific tendinopathies of the shoulder. The results suggest the efficacy of intra-articular FP3 System® multifrequency laser treatment combined with SINOVIAL HL infiltrations in treating patients suffering from calcific tendinopathy of the shoulder, with or without prior percutaneous dissolution of calcifications, proving sufficient on its own for the resolution of acute disease.

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 HL is a medical device consisting of pre-filled syringe containing 3.2% or 4.5% of highly purified sodium hyaluronate, with high and low molecular weight and with visco-elastic properties. These two concentrations of SINOVIAL HL 3.2% and 4.5% are designed to integrate with the synovial fluid, allowing the restoration of the physiological and rheological properties of small - large joints . In addition clinical data have demonstrated that SINOVIAL HL 3.2%, in combination with the laser therapy, can improve the symptomatology correlated to the tendinopathy.

An important characteristic of this product regards its functional ingredient, Hyaluronic acid, since it is present with two different molecular weights, high and low, that interact each other providing unique e rheological characteristics to the device, allowing the administration of higher concentrations of hyaluronic acid at the equal level of viscosity.

As reported in the paragraphs above, several studies have been conducted in order to support the safety and the effectiveness of SINOVIAL HL. Therefore, SINOVIAL HL results to be effective in reducing pain sensation and improving mobility due to degenerative diseases (i.e., arthrosis) and post traumatic diseases. Particularly, in terms of pain reduction and joint function improvement with a rapid and persistent effect. Moreover, the results obtained with these studies demonstrate that SINOVIAL HL 3.2% is even superior to PRP therapy in the treatment of knee osteoarthritis and compared to high molecular weight hyaluronic acid up to 6 months of follow-up in obese patients with knee osteoarthritis, maybe due to the major permanence in the site of action and the presence of both high and low molecular weight HA, which resemble the physiological composition of synovial fluid. The device resulted to have the same performance and better benefits achieved of pharmacological therapy with steroid, suggesting that it could be used as a valid alternative therapy to corticosteroid, especially when it is not recommended or contraindicated.

Other studies conducted with the product investigated and confirmed the efficacy in providing rapid pain relief, associated to a minor consumption of anti-inflammatory or analgesics, and in improving articular and physical function in trapeziometacarpal osteoarthritis and gonoartrosis, reducing joint stiffness, since the early first month and up to 6 months of follow-up.

In another study SINOVIAL HL resulted again superior to high molecular weight hyaluronic acid, even in the treatment of hip OA. When SINOVIAL HL is combined with PRP, for the treatment of

hip pathology in femoro-acetabular impingement syndrome, and for the treatment of knee osteoarthritis, it showed major effectiveness compared to HA alone in terms of both early improvement of symptoms and durations of results. Finally, a large study, involving 692 patients, revealed that a single injection of SINOVIAL HL is more effective than placebo in treating pain associated with knee OA, with the salutary effects beginning at one-week post-administration and continuing through the week 24 follow-up period. The treatment was also well-tolerated given the incidence of adverse events, irrespective of classification, were indistinguishable compared to the placebo. When used in combination with laser therapy, SINOVIAL HL infiltrations is effective in treating patients suffering from calcific tendinopathy of shoulders.

Moreover, the data collected for the revised literature also demonstrated the safety and the good tolerability since no severe or life threating adverse events were recorded. The adverse events observed are to be considered from mild to moderate severity and transient, mostly associate to the injection technique rather than the injected substances. In fact, hyaluronic acid chains contained in SINOVIAL HL are both produced through the fermentation, without further chemical transformations, thus having excellent biocompatibility and allowing the natural re-establishment of the viscoelastic properties of the synovial fluid.

Overall, it can be concluded that, based on the results obtained from the clinical studies conducted with the product and the several data obtained from the consolidated use of the device, it is possible to conclude that SINOVIAL HL is overall safe and good tolerated. It is believed that the benefits deriving from the use of SINOVIAL HL outweigh the risks.

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.

Moreover, the Manufacturer plans for the next year to finalize one clinical investigation to confirm efficacy and safety of the medical device SINOVIAL HL for the treatment of tendinopathies. When this study is completed, the paragraph 5.2 will be updated.

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 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 is another injectable option of treatment providing 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 intraarticular 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 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 has developed SINOVIAL HL with its peculiar formula, belongs to the last generation of treatment for osteoarthritis. This medical device is designed to integrate the synovial fluid, allowing to restore the physiological and rheological properties of the arthritic joints. In particular, clinical data have demonstrated that SINOVIAL HL 3.2%, in combination with the laser therapy, can improve the symptomatology correlated to the tendinopathy . SINOVIAL HL 4.5% is a medical device restores the physiological and rheological properties of the large arthritic joints.

7. Suggested profile and training for users

IBSA Institut Biochimique SA, the Head Quarter of IBSA Farmaceutici Italia srl, manufacturer of SINOVIAL HL, 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 intra-articular 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 11138-4:2017	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 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)
• ISO 11040-8:2016	Prefilled syringes Requirements and test methods for finished prefilled syringes
• 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)