SUMMARY OF SAFETY AND CLINICAL PERFORMANCE
(for patients)

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

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 information presented below is intended ***for patients or lay persons****. A more extensive summary of its safety and clinical performance is prepared for healthcare professionals.*

The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an Implant card or the Instructions For Use to provide information on the safe use of the device

SUMMARY

Revision History

SSCP revision number	Data issued	Change description	Revision validated by the Notified Body
Rev. 0	02/2022	First issue of SSCP according to the Technical File.	Not yet. Validation language: English.
Rev. 1	04/2022	Revision due to the Non-Conformity	Validated Validation language: English

1. Device identification and general information

- 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

- Manufacturer's name and address

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

- Manufacturer's single registration number (SRN)

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

- Basic UDI-DI

The basic UDI, for this medical device, 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.

- Year when the device was first CE-marked

This device is certified since 2015. 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).

2. Intended use of the device

- Intended purpose

HILOW VISCO-SUPPLETIVE JOINT DEVICE with its particular formula belongs to the latest generation of intra-articular treatments and is specifically designed for viscosupplementation with a high concentration of hyaluronic acid without high viscosity is recommended. Thanks to a specific and patented treatment of the solution, the high and low molecular weight of hyaluronic acid present in the device interact with each other giving the solution physical characteristics (rheological properties) such as to obtain viscosity values lower than those of only hyaluronic acid at the same concentration. Indeed, HILOW VISCO-SUPPLETIVE JOINT DEVICE is a medical device designed to integrate the synovial fluid, which allows restoring the physiological properties of arthritic joints. . HILOW VISCO-SUPPLETIVE JOINT DEVICE reduces pain in the joint and encourages recovery of the associated joint. . 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.

- Indications and intended patient groups

INDICATION:

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, only for 3.2%, small joints.

TARGET POPULATION:

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.

- 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

- Device description and material/substances in contact with patient tissues

The device HILOW VISCO-SUPPLETIVE JOINT DEVICE consists of a pre-filled syringe, containing a physiological solution of hyaluronic acid. Hyaluronic acid (HA) is a polysaccharide (a polymer composed by the aggregation of repeated identical molecules of sugar) naturally present in the human organism, and in particular it is the largest molecular component of synovial fluid and it contributes both viscous (lubricating) and elastic (shock-absorbing) properties which are important in the lubrication and protection of cartilage. The increased friction between joint surfaces and simultaneous erosion of cartilage is determined by the development of osteoarthritis, therefore, the use of intra-articular hyaluronic acid is highly justified to recover the normal viscosity and protective function of synovial fluid.

Hyaluronic acid sodium salt is formed by repetitive chains of disaccharide (paired molecules of sugar) units. The length of the disaccharide chains determines its "molecular weight". HILOW VISCO-SUPPLETIVE JOINT DEVICE is composed of high molecular weight (H-HA, constituted of "long" chains) and low molecular weight (L-HA constituted of "short" chains) of hyaluronic acid. The high- and low-molecular-weight of hyaluronic acid used in the device are obtained by biofermentation (produced by the fermentation of a safe bacterial strain) and have not undergone chemical modification processes; this results in excellent tolerability of the product.

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 an expert health care professional.

- Information about medicinal substances in the device, if any

No medicinal substance is present in the device.

- Description of how the device is achieving its intended mode of action

The hyaluronic acid chains with different molecular weight (high and low) present in HILOW VISCO-SUPPLETIVE JOINT DEVICE interact with each other thanks to a specific and patented treatment of the solution (NAHYCO® Hybrid Technology), giving HILOW VISCO-SUPPLETIVE JOINT DEVICE unique

properties that allow higher concentrations of hyaluronic acid to be administered in order to obtain viscosity values lower than those of only hyaluronic acid at the same concentration.

- Description of accessories, if any

No accessories are provided 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).

4. Risks and warnings

It is very important to contact your healthcare professional if you believe that you are experiencing side effects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your healthcare professional if needed

- How potential risks have been controlled or managed

The Manufacturer, through expert teams have monitored all risks that could be associated to the use, design, manufacturing, product's indications, use and misuse, clinical effects and the possible adverse events. In conclusion, it is possible to state that the benefit derived from the use of HILOW VISCO-SUPPLETIVE JOINT DEVICE are higher compared to products use risks, which can be considered acceptable. In addition, the Manufacturer, continuously monitors all potential risks associated to the products, also evaluating those retrieved during the post marketing phase. Risk Assessment is systematically reviewed to ensure that HILOW VISCO-SUPPLETIVE JOINT DEVICE is conform to the progress of technology.

- Remaining risks and undesirable effects

There are some risks that are defined intrinsic, since it is impossible to eliminate or avoid. However, these remaining risks are continuously monitored by the Manufacturer. The undesirable effects related to the injection procedure or due to the characteristics of the products are reported below.

Side-effects:
Extra-articular infiltration of HILOW VISCO-SUPPLETIVE JOINT DEVICE may locally cause undesirable effects. During use of HILOW VISCO-SUPPLETIVE JOINT DEVICE, symptoms such as pain, sensation of heat, reddening or swelling may occur at the injection site. These secondary manifestations can be relieved by applying ice on the treated area. They generally disappear after a short period of time.
It is important you inform your physician/specialist about any undesirable effects occurring after the treatment.
Since the launch of the product (2015) up to 2020, HILOW VISCO-SUPPLETIVE JOINT DEVICE showed a very low incidence of adverse events taking into consideration the total adverse events received (8) in comparison to the total patients exposed (95.142).
The analysis of the collected adverse events is in line with the product's profile: the majority of them are injection site reactions (pain, swelling, erythema, bruising), generally mild and transient that do not require any medication treatment and local signs or symptoms of pain and inflammation (redness, swelling, heating), that may be considered flare-ups of the underlying disorder (knee osteoarthritis) -the patients suffered from- triggered by the intra-articular injection.

- Warnings and precautions

Contra-indications:
HILOW 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.

WARNINGS:
- 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 resterilise. 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

- Summary of any field safety corrective action, (FSCA including FSN) if applicable

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

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

- Clinical background of the device

HILOW VISCO-SUPPLETIVE JOINT DEVICE, 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, designed to integrate with the synovial fluid, allowing the restoration of the properties of joints . In the joint, HILOW - VISCO-SUPPLETIVE JOINT DEVICE 4.5%, is indicated in cases of pain or reduced mobility due to degenerative diseases (e.g., arthritis), post-traumatic diseases associated with acute and chronic joint disabilities in large joints. Considering HILOW - VISCO-SUPPLETIVE JOINT DEVICE 3.2%, it is indicated in cases of pain or reduced mobility due to degenerative diseases (e.g., arthritis), post-traumatic diseases associated with acute and chronic joint disabilities in large and small joints. In addition, HILOW VISCO-SUPPLETIVE JOINT DEVICE 3.2%, in combination with the laser therapy, can improve the symptoms due to the tendinopathy.
Several treatment options are available for the management of osteoarthritis, although none can cure the condition. Over the last few decades, there has been an ongoing trend to use intra-articular injections of either corticosteroids, analgesics/anti-inflammatory drugs, polymerized collagen, anti-cytokine drugs, or hyaluronic acid (viscosupplementation) as alternative modalities to maximise the topical effect and minimise the systemic adverse effects [1].
Viscosupplementation is a therapeutic method by which a viscoelastic solution is injected into the intra-articular space of the joint to replace or reinforce the rheological and protective properties of the synovial fluid, decrease pain and improve joint functionality. The main benefits of viscosupplementation are attributable to its ability to restore the viscoelastic behaviour of synovial fluid in terms of joint lubrication, shock absorption, and reducing mechanical stress on the joint [2,3].

Numerous researches (meta-analyses) have investigated the evidence for the efficacy of hyaluronic acid in treating the symptoms of knee osteoarthritis [4-10] and it has been concluded that hyaluronic acid is an effective intervention in treating knee osteoarthritis without particular adverse events [11-12], being recommended by the Osteoarthritis Research Society International (OARSI) guidelines. [13].
In 2006 was published an analysis of 76 clinical studies conducted with different hyaluronic acid products mostly administered at weekly intervals for 3–5 weeks, in comparison with product without hyaluronic acid (placebo) and other standard treatments (corticosteroids, NSAIDs) reporting that hyaluronic acid can offer a good benefit risk balance for the treatment of osteoarthritis. [14].
Regarding the hyaluronic acid viscosupplementation for the treatment of tendinopathies, several studies have been performed to evaluate the efficacy of hyaluronic acid on adhesions, gliding resistance, and tendon healing [15, 17-19].
After several decades of use, the safety of the administration of hyaluronic acid into the synovial cavity is generally recognised as a safe treatment [20]. It is reported that there are more than 80 marketed intra-articular hyaluronic acid-based products similar to HILOW VISCO-SUPPLETIVE JOINT DEVICE preparations.
This product is on the market from several years, with a good profile of safety and effectiveness. (performance). It is possible to state that non-modified (linear) hyaluronic acid for intraarticular diseases, as HILOW - VISCO-SUPPLETIVE JOINT DEVICE, are widely adopted in the clinical practice and showed appreciable safety profiles.

- The clinical evidence for the CE-marking

Several clinical data have been conducted on HILOW VISCO-SUPPLETIVE JOINT DEVICE to verify and confirm the clinical safety and performance.
In details HILOW - VISCOSUPPLETIVE JOINT DEVICE 4.5% is indicated in association with acute and chronic joint disabilities in large joints, while HILOW - VISCO-SUPPLETIVE JOINT DEVICE 3.2% is indicated aassociated with acute and chronic joint disabilities in large and small joints. 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 [21].
The increased friction between joint surfaces and simultaneous erosion of cartilage is determined by the development of the osteoarthritis disease, therefore, the intra-articular of hyaluronic acid is used to recover the normal viscosity and protective function of synovial fluid.
Several clinical data have been conducted on HILOW VISCO-SUPPLETIVE JOINT DEVICE to verify and confirm the clinical safety and performance of the product.
Overall, HILOW - VISCO-SUPPLETIVE JOINT DEVICE resulted to be effective in reducing pain sensation and improving mobility due to degenerative diseases (arthrosis), post-traumatic diseases, and also in tendinopathy disease when used in combination with laser therapy [21-29].
In particular, patients with degenerative cartilage lesions of the knee treated with HILOW - VISCO-SUPPLETIVE JOINT DEVICE 3.2% responded positively of the treatments, both when compared to patients treated with Platelet Rich Plasma [24] and also when in combination with platelet rich plasma

treatment, giving positive results in terms of pain reduction and joint function improvement with a rapid and persistent effect, up to a maximum of 12 months [25].
Moreover, HILOW - VISCO-SUPPLETIVE JOINT DEVICE has demonstrated to be even superior when compared to high molecular weight hyaluronic acid (SINOVIAL 1.6%, another product of IBSA Farmaceutici with similar indications) [23] up to 6 months of follow-up, maybe due to the major permanence in the site of action and the presence of both high and low molecular weight hyaluronic acid, which resemble the physiological composition of synovial fluid.
Other studies conducted on HILOW - VISCO-SUPPLETIVE JOINT DEVICE sustain the efficacy of the product in providing rapid pain relief, associated to a minor consumption of anti-inflammatory or analgesics, and in improving articular and physical function when injected in the hand (trapezius-metacarpus) [26] and in the knee [27], reducing joint stiffness, since the early first month and up to 6 months of monitoring.
The device resulted again superior to high molecular weight hyaluronic acid, even in the treatment of hip osteoarthritis [29]. In some studies, [25, 28] HILOW - VISCO-SUPPLETIVE JOINT DEVICE was combined with platelet-rich plasma (PRP), for the treatment of hip pathology in femoro-acetabular impingement syndrome, and for the treatment of knee osteoarthritis and the medical device under evaluation demonstrated the efficacy and the major effectiveness respect to HA alone in terms of both early improvement of symptoms and durations of results.
The device resulted to have the same performance of pharmacological therapy with steroid when injected in the hand (trapeziometacarpal joint TMJ, by suggesting that it could be used as a valid alternative therapy to corticosteroid, especially when it is not recommended or contraindicated [22].
In a very large study, 692 patients with pain due to knee osteoarthritis were casually assigned to receive a placebo or HILOW - VISCO-SUPPLETIVE JOINT DEVICE. The results confirmed the efficacy of the device to reduce pain in symptomatic knee, one-week post-administration and continuing through week 24. Both treatments were well tolerated in relation to the adverse events occurred [12].
Therefore, all clinical studies conducted by experts demonstrated that HILOW VISCO-SUPPLETIVE JOINT DEVICE, as well as hyaluronic acid intra-articular injections in general, are effective at reducing pain and restoring joint mobility also in tendon with laser therapy, demonstrating that the treatment is beneficial to patients.

- Safety

HILOW VISCO-SUPPLETIVE JOINT DEVICE resulted to be effective in reducing pain and restoring joint mobility in case of degenerative diseases (e.g. osteoarthritis) and post-traumatic conditions.
Data collected on injections of hyaluronic acid demonstrated the safety and the good tolerability of HILOW VISCO-SUPPLETIVE JOINT DEVICE when injected intra-articularly and used according to indication. No severe or relevant treatment-related side effects were enregistered in all the analysed studies. Moreover, no cases of severe allergic or anaphylactic reactions were observed in any study conducted on the device. No significant adverse effects were reported, and no injection-site ecchymosis or hematomas have been observed.

The safety profile is also enhanced because the hyaluronic acid contained in HILOW VISCO-SUPPLETIVE JOINT DEVICE is obtained through fermentation by bacteria, without any other chemical modifications, with a very safety profile.
The Manufacturer keeps collecting data through analysis from the market and clinical studies for monitoring the safety and the performance of the products, in relation to the indications of use reported in the leaflets.
Other clinical experience conducted with HILOW VISCO-SUPPLETIVE JOINT DEVICE has been demonstrated their safety use when injected in the face and body without no relevant side effects [12, 21-29].
This product is on the market from several years, with a good profile of safety and performance. It is possible to state that to HILOW VISCO-SUPPLETIVE JOINT DEVICE as in general injections of hyaluronic acid for intraarticular diseases are widely adopted in the clinical practice and showed appreciable safety profiles.

6. Possible diagnostic or therapeutic alternatives

- General description of therapeutic alternatives

Osteoarthritis occurs when the cartilage cushioning the ends of bones in joints gradually deteriorates. Different treatment options are available for the management of pain and reduced mobility caused by this disease, although none can cure the condition. The choices of the better strategy to manage symptoms are relative to different factors such as the severity of the disease and the type of articulation.
Less invasive therapies such as aerobic exercise, self-management programs, weight loss, shock-absorbing footwear and oral drugs (analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS)) are the preferred management methods in cases of the disease is in the first steps of severity. These treatments help to relieve symptoms and improve function.
Treatments such as exercise and weight loss often help to reduce the pain however it is often necessary to take pharmacologic analgesics in parallel [16].
When the disease is in progress, treatment options chosen are intra-articular injections and surgery (joint arthroplasty). This latter treatment is used in the end- stage of the disease when no other procedures or therapies have been efficient.
About the treatment for tendon injuries (tendinopathies), no gold standard for the management of this clinical condition is documented, given the controversial clinical results between various studies conducted during the last few years. . The list of currently available interventions for tendinopathy include surgery, nonsteroidal anti-inflammatory drugs, corticosteroids, shockwave therapy, and the injection of a lot of type of substances in the tendon area such as platelet-rich plasma injection. Additionally, peritendinous injections of hyaluronic acid (HA) seems to be an effective experimental therapeutic option for the management of chronic tendinopathy (viscosupplementation)

However, when considering alternative treatments, it is recommended to contact your healthcare professional who can take into account your individual situation.

7. Suggested training for users

The products must be injected by expert healthcare professional. IBSA continuously plans and performs training dedicated to injectors.

8. References

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