Summary of safety and clinical performance

Hyaluronan Soft Tissue Filling Gel
Aqualuna Aqua

Basic UDI-DI: 69480604HX0011HY

APPROVAL

Function/Role	Name	Signature	Date
Prepared by			
Reviewed by			
Authorized by			

REVISION HISTORY

Revision; Date	**Description of change(s)**	**Author**
1.0; September 2024	New document	Yan Zhang
2.0; March 2025	Update of the EMDN code and addition of harmonized standards	

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PART 1: INTENDED FOR THE HEALTHCARE PROFESSIONALS

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 Hyaluronan Soft Tissue Filling Gel.

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**.

1 DEVICE IDENTIFICATION AND GENERAL INFORMATION

1.1 Device trade name(s)

Aqualuna Aqua

1.2 Manufacturer's name and address

Bloomage Biotechnology Corp., Ltd.
No. 678 Tianchen St., High-Tech Development Zone, Jinan, Shandong, China
Website: http://www.biohyalux.com

1.3 Manufacturer's single registration number (SRN)

CN-MF-000013641

1.4 Basic UDI-DI

69480604HX0011HY

1.5 Medical device nomenclature description/ text

European Medical Device Nomenclature (EMDN): X0303 - Substances, combinations of substances, or items without an intended medical purpose intended to be used for facial or other dermal or mucous membrane filling by subcutaneous, submucous, or intradermal injection or other introduction, by a prefilled means for introduction, excluding those for tattooing - Resorbable

1.6 Class of device:

Class III

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

2025

1.8 Authorised representative if applicable; name and SRN

Name: WellKang Ltd.
SRN: XI-AR-000001836

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

NB's Name: BSI Group The Netherlands B.V.
NB's single identification: 2797

2 INTENDED USE OF THE DEVICE

2.1 Intended purpose

The Hyaluronan Soft Tissue Filling Gel is intended to be used on facial dermal tissue to correct forehead wrinkles.

2.2 Indication(s) and target population(s)

2.2.1 Indication

The Hyaluronan Soft Tissue Filling Gel is indicated for correcting mild to severe forehead wrinkles.

2.2.2 Target population

Hyaluronan Soft Tissue Filling Gel is intended for adults (over 18 years old), both men and women, with mild to severe forehead wrinkles.

2.3 Contraindications and/or limitations

- Product should not be used in persons who are less than 18 years old.
- Product should not be used in patients allergic to hyaluronic acid or with a history of severe allergic reactions.
- Do not use in patients with known hypersensitivity to lidocaine and amide-type local anaesthetics.
- Product should not be used in patients with bleeding disorders (i.e. coagulopathy), patients receiving any thrombolytic agent, anticoagulant or platelet aggregation inhibitor within two weeks and in menstruating, pregnant or lactating women.
- Product should not be used on or around damaged or inflamed skin due to skin disease, infection or similar conditions.
- Product should not be used together with any other implantable or injectable product within 6 months.
- Product should not be used in patients who undergo laser treatment, chemical peeling or any skin-irritating therapies before confirmed fully skin healing or within 1 month after implantation of this product to avoid possible inflammatory reactions.

3 DESCRIPTION OF THE DEVICE

3.1 General description of the device

The Hyaluronan Soft Tissue Filling Gel is a device with a non-medical purpose, which is intended to be used on facial dermal tissue to correct mild to severe forehead wrinkles of adults. Hyaluronan Soft Tissue Filling Gel repairs and corrects the skin structure and improves the elasticity of the skin with an expected resorption period of 3 to 6 months. Additionally, the lidocaine hydrochloride reduces the pain of the injections.

Each packaging contains one a 1 mL prefilled syringe and two single-use CE certified 30G×1/2" (0.3 x 12 mm) stainless steel needles. The composition of the gel of Hyaluronan Soft Tissue Filling Gel contains 12 mg/mL cross linked sodium hyaluronate responsible for the main intended use and 3 mg/mL lidocaine hydrochloride to reduce the pain of the injection. Additionally, the gel of Hyaluronan Soft Tissue Filling Gel also contains 9 mg/mL Sodium chloride, 0.05 mg/mL sodium dihydrogen phosphate monohydrate, 0.22 mg/mL dibasic sodium phosphate and further water for injection.

3.2 Previous generation(s) or variants if such exist, and a description of the differences

During the development, Hyaluronan Soft Tissue Filling Gel has been used as name and outside the European Union (EU) the product is marketed as Dermallure™ Hydra.

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

There are no accessories for Hyaluronan Soft Tissue Filling Gel.

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

The Hyaluronan Soft Tissue Filling Gel is used in combination with the packed single-use CE certified 30G×1/2" (0.3 x 12 mm) stainless steel needles to be able to perform the treatment procedure and thus the injection by the healthcare professional.

4 RISKS AND WARNINGS

4.1 Residual risks and undesirable effects

Local reactions related to the injection include immune responses, skin pigmentation, hardening, nodules, and injection site reactions. Injection site reactions (swelling, tenderness, pain, redness, pruritus, bruising) within 7 days after injection are primarily mild to moderate and resolve or disappear 1 month after injection. More severe complications could be facial nerve injury, syncope and blindness with improper injection, or even death. Hypersensitivity or allergic reactions for one of the ingredients have been rarely observed. The symptoms include swelling, edema, pruritus and rarely reported papules in the surrounding tissues and even more severe symptoms as urticaria and granulation formation. Patients who experience these severe hypersensitivity or allergic reactions should not be retreated.

4.2 Warnings and precautions

- Only to be administered by appropriately trained healthcare professionals who are qualified or accredited in accordance with national law.
- Do not resterilise.
- Do not re-use to avoid infection.
- Do not use if package is damaged.
- Product is only for intradermal injection. Do not inject intravenously.
- Do not use after expiry date.
- The aseptic operating procedures for surgical treatment should be strictly followed in the process of injection and local disinfection of injection site is required to avoid infections.
- Do not expose the injection site to extreme temperatures (e.g. high temperatures such as sunbathing or extremely cold environments) and avoid massage and facial mask care within 7 days following the implantation by injection.
- Patients who are using substances that affect platelet function, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.
- Lidocaine should be used with caution in patients with epilepsy, renal or liver insufficiency, block of cardiac conduction system, patients with reduced cardiovascular function, or with bradycardia.
- Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain anti-arrhythmics, since the systemic toxic effects can be additive.

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

No Field Safety Corrective Actions have ever been required.

5 SUMMARY OF CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP

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

Not applicable.

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

A prospective, multi-center, single-blind, randomized, parallel controlled clinical study has been performed in 2017 to demonstrate the safety and performance of Hyaluronan Soft Tissue Filling Gel for the treatment of moderate to severe frontal wrinkles within adults.

Identity of the investigation	Prospective, multi-center, single-blind, randomized, parallel controlled clinical study of the safety and effectiveness of Hyaluronan Soft Tissue Filling Gel for the treatment of frontal wrinkles. 2017, China.
Identity of the device including any model number/version	Hyaluronan Soft Tissue Filling Gel.
I Intended use of the medical device used in the investigation	The Hyaluronan Soft Tissue Filling Gel is intended to be used on facial dermal tissue to correct forehead wrinkles.
Objectives of the study	Verify the effectiveness and safety of Hyaluronan Soft Tissue Filling Gel in the treatment of moderate to severe frontal wrinkles.
Study design	This is a prospective, multi-center, single-blind randomized, parallel controlled clinical study.
Endpoints	<u>Primary effectiveness endpoints:</u> 1. Non-inferiority of Hyaluronan Soft Tissue Filling Gel's Wrinkle Severity Rating Scale (WSRS) responder rate when compared to medical hydroxypropyl methylcellulose (medical HPMC), a sodium hyaluronate solution (control treatment) at 6 months after treatment. Subjects with frontal wrinkles are considered responders if, after injection of the test product, the WSRS score of the frontal wrinkles is reduced by at least one grade compared with pre-treatment. The percentage of the total number of experiments is the responder rate. 2. Visual analogue scale (VAS, where 0 = no pain and 10 = the most severe pain) superiority of Hyaluronan Soft Tissue Filling Gel when compared to control treatment at 6 months after treatment <u>Secondary effectiveness endpoints:</u> 1. WSRS responder rate was evaluated immediately, 7 days, 30 days, 3 months, 9 months and 12 months after treatment. 2. Global Aesthetic Improvement Scale (GAIS, were 1 = Very much improved and 5 = Worse) responder rate was evaluated immediately, 7 days, 30 days, 3 months, 9 months and 12 months after treatment. <u>Primary safety endpoints:</u>

	1. Vital signs (i.e. blood pressure, heart rate, body temperature and respiration, 12-lead electrocardiogram [ECG]), laboratory examination (i.e. blood routine, urine routine, biochemical examination, and four coagulation tests) and occurrence of adverse events.
Inclusion/exclusion criteria	Inclusion Criteria: For each subject, all of the following 3 criteria should be reached: 1. 18-65 years old; 2. With moderate to severe frontal or forehead wrinkles (with score of 3 or 4) graded by investigators according to WSRS (1 absent, 2 mild, 3 moderate, 4 severe and 5 extreme); and 3. Signed a written Informed Consent Form voluntarily, and agree to be followed up. Exclusion Criteria Subjects reaching one of the following exclusion criteria were excluded: 1. Local damage of forehead, or other active skin disease; 2. Known to be allergic to local anaesthetics, especially to lidocaine; 3. Suspected to be allergic to Hyaluronic Acid (HA)-based products; 4. History of severe allergic reactions, or be allergic to a variety of substances and shown severe allergic reactions; 5. The patients who had received botulinum toxin injection, other dermal filling, chemical peeling, laser and other frontal rhytidectomy within one year; 6. Have taken facial lifting surgery previously; 7. Liver function parameters（alanine transaminase; ALT, aspartate aminotransferase; AST）fall beyond the normal range; 8. Creatinine beyond the normal range; 9. Subjects with abnormal coagulation mechanism, or subjects who have received thrombolysis agent, anticoagulant or platelet coagulation inhibitor within 2 weeks; 10. Subjects who need to use a mixture of other products, including the following situations: facial injection of permanent filler or facial use of non-permanent filler within 12 months; 11. Patients with autoimmune diseases, immune dysfunction or serious diseases of important organs; 12. Subjects with malignant tumors and end-stage diseases; 13. Female subjects in pregnancy or lactation; 14. Not suitable for the study according to decision of the investigator; or 15. Those who participated in clinical trials of other drugs or medical devices before enrolment but failed to reach the time limit of primary endpoint.
Number of enrolled patients	In this study, 180 subjects (test group: n = 89, control group: n = 91) were enrolled, of which 165 subjects completed 12 months follow-up, 15 cases dropped out resulting in a drop-out rate of 8.3%.
Study population	The sex ratio of the subjects in this study was 34.83% males and 65.17% females in the test group, 37.78% males and 62.22% females in the control group. The age was 44.90±11.30 years old in the test group and 45.21±10.01 years old in the control group. One subject in the test group

	and 4 subjects in the control group had received frontal cosmetic treatment, 2 subjects in the test group had received facial cosmetic surgery, and 2 subjects in the control group had used frontal non-permanent fillers. There were no statistically significant differences between the two groups in the demographic characteristics, vital signs, and general clinical data.
Summary of the study methods	In this study, 180 subjects were included. The subjects were randomized (making use of SAS® 9.1.3 software) to one of the following two treatment groups: Hyaluronan Soft Tissue Filling Gel group (Test group) and the medical HPMC group (Control group). Subjects underwent a screening visit and completed an examination (visit 1) maximum 7 days before treatment with Hyaluronan Soft Tissue Filling or medical HPMC at the baseline or treatment visit (visit 2, day 0). During the treatment visit the selected product was visually inspected and the injection site was disinfected before injection to minimize risk of adverse events due to infection. Then the dermal filler was injected in the dermal tissue (a maximum of 10 injection points in one patient) following treatment procedure detailed in the Instructions For Use of each product. Follow-up visits were performed after 7 days from treatment (visit 3, post-treatment follow-up), and after 30 days (visit 4), 3 months (visit 5), 6 months (visit 6), and 12 months (visit 7). The responder rate of each subject ’s WSRS and GAIS was evaluated by the subject, the investigator (healthcare professional) and an independent review panel blinded to the subject's enrolment at all timepoints. The review panel also evaluated the photos of each subject in each visit window. The efficacy endpoints WSRS and GAIS are evaluated at all stated timepoints and the VAS solely at 6 months (visit 6) after treatment.
Summary of results	Of the 180 included subjects, 179 were included in the full analysis, 163 in the Per Protocol analysis (Test group: 79 subjects, control group: 84 subjects) and 179 in the Safety analysis. At baseline (time of enrolment) there was no significant difference in static and dynamic frontal wrinkles WSRS between the groups. The primary performance endpoint results showed effectiveness of Hyaluronan Soft Tissue Filling Gel (at least 1-point WSRS improvement in most patients) and non-inferiority of static and dynamic WSRS of the test group over the control group at 6 months when evaluated by the investigator and the independent review panel. Moreover, the difference in the VAS score between the two groups was statistically significant (P value < 0.05), i.e. the intraoperative pain of the test group was less than that of the control group. Thus, the superiority of VAS score of primary effectiveness endpoint was established. Secondary performance endpoints were Wrinkle Severity Rating Scale (WSRS)and global aesthetic improvement scale (GAIS) responder rates measured immediately, at 7 days, 30 days, 3 months, and 12 months. The responder rate of static WSRS over 90% in both groups at 30 days after treatment. Whereas according to the independent review panel the responder rate at 12 months was close to that immediately after treatment in both groups, and therefore effectiveness could be maintained for 12

	months, the investigators and subjects evaluated that the responder rate at 12 months after operation was decreased compared with that after treatment, but still above 60%. There was no significant difference between the two groups in responder rate at immediate, 7 days, 30 days, 3 months and 12 months after operation (P > 0.05). Also GAIS showed no difference between the groups at 12 months after treatment. GAIS was evaluated to be higher after treatment, and whereas the investigators and subjects evaluated that the GAIS then decreased to the lowest score at 12 months after treatment, the independent review panel evaluated that GAIS was higher in both groups, and still improved significantly 12 months after treatment. Safety endpoint results show that there was no significant difference in vital signs (P value > 0.05) and laboratory examinations before and after injection between the two groups. Moreover, results showed no difference in the local and systemic adverse events incidence between the two groups (P value >0.05). The local adverse events related to the device were swelling, tenderness, itching, pain, bruising, congestion, erythema redness, and sensitization, which were mostly mild or moderate. Further, no unexpected device related local adverse events at the injection site, no local adverse events at the injection site leading to drop out, and no serious local adverse events at the injection site were reported in the two groups. Systemic adverse events related to investigational device included 1 case of mild dermatitis in the test group, which was relieved after applying vitamin E emulsion, and one case of mild facial swelling in the control group, which did not require any corrective treatment. No unexpected systemic device related adverse events were found, and there were no systemic adverse events leading to drop out.
Limitations	Not applicable.

5.3 Summary of clinical data from other sources, if applicable

5.3.1 Vigilance data from other regulatory markets

The vigilance data in the other regulatory markets was collected consistently from 2020 to 2023 for Hyaluronan Soft Tissue Filling Gel.

Since 2020, the frequency of incidents of Hyaluronan Soft Tissue Filling Gel every year has been very low (i.e. 0.0% in 2020, 0.0011% in 2021, 0.0003% in 2022, and 0.0011% in 2023). All adverse events were non-serious incidents. The main adverse events were mild to moderate and included the appearance of papule, redness and/or erythema, itching, and swelling. The only severe adverse event was facial skin allergy. Most adverse events disappeared within 1 month after specific treatment of adverse events (e.g. cold spray wet compress treatment, hot compress and massage, etc.).

5.4 An overall summary of the clinical performance and safety

Hyaluronan Soft Tissue Filling Gel is a safe, well tolerated, and effective product to correct temporary mild to severe forehead wrinkles within adults. Only clinical safety and performance data on repeated treatment with Hyaluronan Soft Tissue Filling Gel is limited.

Hyaluronan Soft Tissue Filling Gel improves the elasticity of the skin with an expected resorption period of 3 to 6 months. This has been demonstrated in a clinical investigation, whereby for most patients treated with Hyaluronan Soft Tissue Filling Gel an improvement is observed in dynamic and static Wrinkle Severity Rating Scale (WSRS) and Global Aesthetic Improvement Scale (GAIS), which were both rated by healthcare professionals and subjects, within the first 6 months after injection.

The lidocaine within Hyaluronan Soft Tissue Filling Gel relieves the pain during injections. However, local reactions (immune responses, skin pigmentation, hardening, nodules, and injection site reaction such as swelling, tenderness, pain, redness, pruritus, bruising) within 7 days after injection, which will resolve or disappear within 1 month after injection, are anticipated based on non-clinical *in vitro* and *in vivo* data, the available clinical data, the clinical investigation and collected vigilance data.

5.5 Ongoing or planned post-market clinical follow-up

The planned Post Market Clinical Follow-up (PMCF) activities are limited (i.e. screening of literature). Therefore, the identified PMCF activity has been included in the post market surveillance (PMS) activities.

6 POSSIBLE DIAGNOSTIC OR THERAPEUTIC ALTERNATIVES

Wrinkles are visible creases or folds in the skin caused by skin aging, which is a degenerative phenomenon that impacts the whole population and has an aesthetic impact on the individuals. Skin aging is a complex process that involves intrinsic and extrinsic mechanisms that leads to numerous biological and biochemical changes as well as secondary structural changes of the skin, underlying muscles, subcutaneous fat tissue, and bony structure [1, 2].

There are many treatment options available for wrinkle correction. The different treatments can be classified in three main groups: Energy-based devices, topical agents and injectables.

6.1 Energy-based devices

Lasers, high frequency ultrasound (HFUS), and radiofrequency (RF) devices deliver thermal energy to the reticular dermis and subcutaneous tissue, which subsequently causes tissue contraction and stimulates neocollagenesis, leading to improvement in skin laxity and wrinkles. More recently, fractional RF microneedling (FRFM) devices that deliver targeted bipolar RF energy directly to the reticular dermis via microneedles have been developed, which have the same mode of action as the previously mentioned HFUS and RF devices [2]. These treatments have a good safety profile. The most common adverse effects of energy-based devices (i.e. laser, HFUS and RF devices) are pain and bruising. Some other less common complications include erythema, edema, and swelling while infrequent adverse events include tenderness and temporary paresthesia [3, 4].

6.2 Topical agents

In this category topical treatment options such as retinoids, chemical peeling, and topical antioxidants can be found.

Retinoids and their antioxidant effect are currently considered the most effective topical option to improve skin aging. They have been shown to increase types I, III, and VII collagen and glycosaminoglycan (GAG) deposition (strong positive effect on collagen metabolism) and to normalize elastic tissue organization. Moreover, there is clinical evidence supporting the role of topical retinoids in the reversal of skin aging phenotypes including fine wrinkling, dyschromia, and skin elasticity [2, 5]. Regarding safety, the most common adverse events reported during the use of retinoids are erythema, scaling, dryness, and irritation. The majority of these adverse events reach their maximum intensity within the first two weeks of application and diminish over time [6].

Chemical superficial peeling using topical alpha-hydroxy acids, such as glycolic or lactic acid, have been shown to improve the quality of elastic fibers, stimulate GAG and collagen production in the dermis, and increase the epidermal thickness, helping correct wrinkles [2, 5]. However, these treatments can also lead to adverse events such as erythema and flaking. Skin photosensitivity has also been reported but it is less common. Moreover, studies have shown that with higher product concentrations, side effects are more pronounced [6].

Finally, topical antioxidants, such as ascorbic acid (vitamin C), polyphenols or flavonoids, have also been shown to be effective in reducing wrinkles by reducing collagen degradation and free radicals (FRs) [2, 5]. For example, ascorbic acid reduces ROS and is required for collagen synthesis in

human skin fibroblasts. However, its clinical efficacy can be reduced due to its poor skin penetration and chemical instability [2]. Regarding safety, the most common adverse effects reported during the use of topical antioxidants are skin flaking, erythema and unilateral stinging. This treatment has the mildest adverse effects between the topical agents [6].

6.3 Injectables

Dermal fillers are the main injectable products used for wrinkle correction, however, there are also other injectable treatments in the market such as autologous platelet-rich plasma (PRP) therapy and botulinum toxin (BTX) injections.

Dermal fillers

Dermal fillers are injected within or beneath the skin to improve its physical features by soft tissue augmentation. Its use in the dermatologic field has been increasing to improve wrinkles and restore the soft tissue volume in aged skin [2]. There are three types of dermal fillers: temporary fillers (lasting between 6 months and 2 years), semipermanent fillers (lasting between 2-3 years), and permanent fillers (lasting longer than 3 years) [5, 7].

The most common temporary fillers due to its biocompatibility and ease of use are hyaluronic acid (HA) fillers, which is the case of Hyaluronan Soft Tissue Filling Gel. Further, poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) are the main semipermanent fillers in the market. PLLA fillers have a progressive volumizing effect which begins one week after injection and continues over the course of weeks to months while microparticles of PLLA are slowly metabolized to carbon dioxide and water. These degrading leaves crystal behind, which result in an inflammatory reaction that causes dermal fibroplasia that leads to the desired cosmetic effect. On the other hand, CaHA fillers contain CaHA particles that act as a scaffold for new tissue formation and stimulate collagen formation around the microspheres leading to the thickening of the dermis over time [5, 7]. Finally, polymethylmethacrylate (PMMA) microspheres with collagen is the main permanent filler in the market. PMMA filler injection into the deep dermal layer causes an immediate mechanical filling through the gel. The collagen is absorbed within 1 month, however, PMMA microspheres are not reabsorbed, which cause a long-term neocollagenesis and fibroplasia [7]. All these types of dermal fillers have an acceptable safety profile and lead to similar adverse events (see section 4.1).

Other injectables

Autologous PRP therapy injection leads to the secretion of various growth factors which are known to regulate processes including cell migration, attachment, proliferation and differentiation, and promote ECM accumulation by binding to specific cell surface receptors. Moreover, it has been shown that PRP may induce synthesis of collagen and other matrix components by stimulating the activation of fibroblasts, thus, rejuvenating the skin and helping correct wrinkles [5]. Most common side effects of this treatment are transient post-injection pain and burning sensation in the treated area. Moreover, other less common complications such as erythema and bruising/ ecchymosis at the injection site have been reported too. These side effects are usually temporary and resolve within days or a couple weeks [8].

BTX injections mode of action is different to all previously mentioned injectables. Instead of stimulating collagen synthesis and fibroblasts activation it leads to a clinically reversible chemical denervation and selective muscle relaxation or paralysis 24 to 48h after treatment, which can continue up to 2 weeks. This mode of action makes the treatment useful for management of certain dynamic facial lines and dynamic wrinkles, i.e. facial line and wrinkles formed by facial movements, because it prevents movement, thus, creation dynamic facial line or wrinkles [5]. Most common adverse effects of this treatment are bleeding, swelling, erythema, pain at the injection sites, and headache. Moreover, other less common complications include malaise, nausea, influenza-like symptoms, and ptosis. In patients who undergo BTX injections to treat bunny lines (periorbital) strabismus caused by inadvertent injection of BTX and local diffusion it may appear as a complication too. Nevertheless, all of these side effects gradually resolve after the paralytic effect of the toxin dissipates [9].

7 SUGGESTED PROFILE AND TRAINING FOR USERS

Hyaluronan Soft Tissue Filling Gel is intended to only be administered by appropriately trained healthcare professionals who are qualified or accredited in accordance with national law. Please note that Bloomage Biotechnology Corp., Ltd., manufacturer of Hyaluronan Soft Tissue Filling Gel, organizes training sessions dedicated to these healthcare professionals of different countries aimed at training them on the correct use, including injection technique, of Hyaluronan Soft Tissue Filling Gel. Further, the injections with Hyaluronan Soft Tissue Filling Gel should be performed following aseptic operating procedures for surgical treatment and an explanation is also presented in the section on treatment procedure within the Instructions For Use.

8 REFERENCE TO ANY HARMONISED STANDARDS AND CS APPLIED

Hyaluronan Soft Tissue Filling Gel complies with the requirements of Medical Device Regulation (MDR) 2017/745 resulting in a CE mark and Annex I and IV of the Common Specifications (CSs) of the Commission Implementing Regulation (EU) 2022/2346.

Standard	**Title**
EN ISO 10993-1 and relevant parts	Biological evaluation of medical devices – Part 1: Evaluation and testing within risk management process
EN ISO 11607-1 and -2	Packaging for terminally sterilized medical device – Part 1: Requirements for materials, sterile barrier systems and packaging systems and, – Part 2: Validation requirements for forming, sealing and assembly processes
EN ISO 13485	Medical devices - Quality management systems - Requirements for regulatory purposes
EN ISO 14639	Non-active surgical implants – General requirements
EN ISO 14971	Medical devices – Application of risk management to medical devices
EN ISO 15223-1	Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 1: General requirements
EN ISO 17765	Sterilization of health care products – Moist heat: Requirements for the development, validation, and routine control of a sterilization process for medical devices
EN ISO 20417	Medical Devices – Information to be supplied by the manufacturer
EN IEC 62366-1	Medical Devices – Part 1: Application of usability engineering to medical devices
MEDDEV 2.7.1	Clinical evaluation on medical devices: a guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC

9 REFERENCES TO LITERATURE

Reference	References
[1]	Manríquez JJ, Majerson Gringberg D, Nicklas Diaz C. Wrinkles. BMJ Clin Evid. 2008 Dec 16;2008:1711. PMID: 19445782; PMCID: PMC2907965.
[2]	Shin SH, Lee YH, Rho NK and Park KY. Skin aging from mechanisms to interventions: Focusing on dermal aging. Front Physiol. 2023 May. doi: 10.3389/fphys.2023.1195272. eCollection 2023.
[3]	Ayatollahi A, Gholami J, Saberi M, Hosseini H, Firooz A. Systematic review and meta-analysis of safety and efficacy of high-intensity focused ultrasound (HIFU) for face and neck rejuvenation. Lasers Med Sci. 2020 Jul;35(5):1007-1024. doi: 10.1007/s10103-020-02957-9. Epub 2020 Feb 5. PMID: 32026164.
[4]	Lyu JJ, Sheng-Xiu L. Radiofrequency in Facial Rejuvenation. International Journal of Dermatology and Venereology 5(2):p 94-100, June 2022. | DOI: 10.1097/JD9.0000000000000193
[5]	Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E and Zouboulis CC. Skin anti-aging strategies. Dermatoendocrinol. 2012 Jul 1; 4(3): 308 319.doi: 10.4161/derm.22804.
[6]	Thomas JR, Dixon TK, Bhattacharyya TK. Effects of topicals on the aging skin process. Facial Plast Surg Clin North Am. 2013 Feb;21(1):55-60. doi: 10.1016/j.fsc.2012.11.009. PMID: 23369589.
[7]	Michael LH, David P. Beynet, Nima M. Gharavi. Overview of Deep Dermal Fillers. Facial Plast Surg. 2019 Jun;35(3):224-229. doi: 10.1055/s-0039-1688843.
[8]	Maisel-Campbell AL, Ismail A, Reynolds KA, Poon E, Serrano L, Grushchak S, Farid C, West DP, Alam M. A systematic review of the safety and effectiveness of platelet-rich plasma (PRP) for skin aging. Arch Dermatol Res. 2020 Jul;312(5):301-315. doi: 10.1007/s00403-019-01999-6. Epub 2019 Oct 18. PMID: 31628542.
[9]	Satriyasa BK. Botulinum toxin (Botox) A for reducing the appearance of facial wrinkles: a literature review of clinical use and pharmacological aspect. Clin Cosmet Investig Dermatol. 2019 Apr 10;12:223-228. doi: 10.2147/CCID.S202919. PMID: 31114283; PMCID: PMC6489637.

10 REVISION HISTORY OF SUMMARY OF SAFETY AND CLINICAL PERFORMANCE FOR USERS/HEALTHCARE PROFESSIONALS

SSCP – Part 1 Revision Number	**Date issued**	**Description of change(s)**	**Revision validated by the Notified Body**
1.0	September 2024	New document	☒ No Validation language: English
2.0	March 2025	Update the EMDN code (section 1.5), update of year when the first certificate was issued covering the device (section 1.7) and harmonized standards (section 8);	☐ Yes Validation language: English

PART 2: INTENDED FOR PATIENTS

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 prepared for healthcare professionals is found in the first part of this document.

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 a Patient leaflet to provide relevant safety information of Hyaluronan Soft Tissue Filling Gel.

1 DEVICE IDENTIFICATION AND GENERAL INFORMATION

1.1 Device trade name

Aqualuna Aqua

1.2 Manufacturer's name and address

Bloomage Biotechnology Corp., Ltd.
No. 678 Tianchen St., High- Tech Development Zone, Jinan, Shandong, China
Website: http://www.biohyalux.com

1.3 Basic UDI-DI

69480604HX0011HY

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

2025

2 INTENDED USE OF THE DEVICE

2.1 Intended purpose

The Hyaluronan Soft Tissue Filling Gel is intended to temporarily smooth out the forehead facial wrinkles after one or more injections. Hyaluronan Soft Tissue Filling Gel is restoring a natural, soft look to your forehead and to improve the skin elasticity.

2.2 Indication(s) and intended patient groups

2.2.1 Indication

As you age, your facial skin begins to lose its elasticity and volume. As a result, the lines on your forehead become more pronounced. The Hyaluronan Soft Tissue Filling Gel is indicated for correcting mild to severe forehead wrinkles.

2.2.2 Intended patient groups

Hyaluronan Soft Tissue Filling Gel is intended for adults (over 18 years old), both men and women, with mild to severe forehead wrinkles.

2.3 Contraindications

You should not use Hyaluronan Soft Tissue Filling Gel if you:

- Are below 18 years old
- Have severe allergies with a history of severe reactions (anaphylaxis)
- Are allergic to hyaluronic acid
- Are allergic to the anaesthetic lidocaine or to amide-type of anaesthetics
- Have any blood clotting disorders
- Have any skin disorders, history of developing scarring, skin inflammation or skin infections
- Have had another implantable or injectable in the last 6 months
- Have had recently a laser treatment, chemical peel or any procedure which may cause your skin to be irritated before confirmed healing
- Are pregnant, breast-feeding or on your period
- Lidocaine should be used with caution if you have epilepsy, kidney, liver or heart problems

You must be over 18 years of age to receive Hyaluronan Soft Tissue Filling Gel.

If you are not sure about your medical history concerning these allergies, please discuss further with your doctor.

3 DEVICE DESCRIPTION

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

Hyaluronan Soft Tissue Filling Gel contains hyaluronic acid, which is a naturally occurring substance in your body, and will temporarily smooth out the forehead facial wrinkles after one or more injections. Hyaluronan Soft Tissue Filling Gel is restoring a natural, soft look to your forehead.

3.2 Information about medicinal substances in the device, if any

Hyaluronan Soft Tissue Filling Gel contains a medicine, 3 mg/ml lidocaine. Lidocaine is a commonly used local anaesthetic used to numb the area during the injection(s).

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

Hyaluronan Soft Tissue Filling Gel contains hyaluronic acid, which is a naturally occurring substance in your body, and will temporarily smooth out the forehead facial wrinkles after one or more injections. The healthcare professional may gently rub the treated area to allow the product to integrate with the surrounding tissues. Hyaluronan Soft Tissue Filling Gel has been shown to be effective up to 6 months after injection.

3.4 Description of accessories, if any

There are no accessories for Hyaluronan Soft Tissue Filling Gel.

4 RISKS AND WARNINGS

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.

4.1 How potential risks have been controlled or managed

Bloomage Biotechnology Corp., Ltd. have conducted a clinical study with Hyaluronan Soft Tissue Filling Gel on patients, reviewed published scientific literature of similar products on the market, analysed feedback from both healthcare professionals and patients of Hyaluronan Soft Tissue Filling Gel and compared those collected data with similar products on the market. Where risks exist, the product has been re-evaluated to see if the design can be changed so that the risk is reduced or no longer exists. If this is not possible, information is listed in the instructions for the healthcare professional to be made aware of, and also in the Patient leaflet so that the patient is also aware.

4.2 Remaining risks and undesirable effects

Common side effects, likely to appear during the first week, are:

- Swelling
- Tenderness
- Pain
- Redness
- Bruising

These will likely resolve 1 month following the procedure. Note that in case of swelling in the treated area immediately after injection, an ice pack can be applied for a short period.

Less common side effects are:

- Infection
- Skin discoloration
- Filler migration
- Facial nerve injury
- Fainting
- Blindness
- Allergic reaction, which may be recognized by swelling, fluid build-up, itching, skin lesions, rash or hives
- Death

You should tell your healthcare professional immediately if you experience any of these side effects or if you notice anything unusual at the site of treatment.

4.3 Warnings and precautions

The following are important considerations for you to discuss with your healthcare professional and understand in order to help avoid unsatisfactory results and complications:

- Once you have undergone your procedure, it is important to avoid extremely warm (saunas, sunbathing) or cold temperature environments.
- Do not have massages or use face masks for 7 days after the procedure.
- Do not have, within 1 month after injection, a laser treatment, chemical peel or any procedure which may cause your skin to be irritated.
- You may bruise or bleed more if you are taking certain medication such as aspirin or non-

steroidal anti-inflammatory drugs.

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

No major safety concerns have been reported, nor any Field Safety Corrective Actions have ever been required.

5 SUMMARY OF CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP

5.1 Clinical background of the device

The most common temporary dermal fillers due to its biocompatibility and ease of use are with hyaluronic acid. Additionally, due to the pain experienced caused by the injection(s) performed by a healthcare professional a local anaesthetic as lidocaine is often used either separately or as part of the dermal filler. Hyaluronan Soft Tissue Filling Gel does not contain novel design features and therefore there is a proven clinical track record of safety and performance of similar products on the market.

5.2 The clinical evidence for the CE-marking

Clinical evidence for CE-marking to confirm the safety and performance profile of Hyaluronan Soft Tissue Filling Gel is based on laboratory testing, a clinical investigation, and market feedback from outside the European Union. During the clinical investigation 89 subjects received Hyaluronan Soft Tissue Filling Gel, who reported that Hyaluronan Soft Tissue Filling Gel can satisfactorily correct moderate to severe forehead wrinkles within the first 6 months.

5.3 Safety

Minimal safety concerns are reported during the clinical investigation and market feedback from outside the European Union. Thus, Hyaluronan Soft Tissue Filling Gel is safe and well tolerated in adults of 18 years and older with a proven temporary performance effect to correct moderate to severe forehead wrinkles. The safety and performance data on repeated treatments is limited. More long-term and repeated safety and performance data with Hyaluronan Soft Tissue Filling Gel will be collected via experiences on the market with Hyaluronan Soft Tissue Filling Gel.

6 POSSIBLE DIAGNOSTIC OR THERAPEUTIC ALTERNATIVES

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

6.1 General description of therapeutic alternatives

As you age, your facial skin begins to lose its elasticity and volume. As a result, the lines on your forehead become more pronounced. Hyaluronan Soft Tissue Filling Gel contains hyaluronic acid, which is a naturally occurring substance in your body, and will temporarily smooth out the forehead facial wrinkles after one or more injections. Hyaluronan Soft Tissue Filling Gel is a so-called dermal filler, which is injected into your skin. There are alternative treatment options available, which can be either injectable (dermal fillers or other), applied to the surface of your skin, or deliver heat into the skin by applying energy.

6.1.1 Injectables

Dermal fillers can be roughly divided in three groups based on how their effects will last:

- temporary, lasting between 6 months and 2 years;
- semipermanent, lasting between 2-3 years; or
- permanent, lasting longer than 3 years.

The most common temporary fillers are made of a substance known as hyaluronic acid, which is the case of Hyaluronan Soft Tissue Filling Gel. Semipermanent fillers include those composed of substances called poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA). Polymethylmethacrylate (PMMA) microspheres is a well-known permanent dermal filler. All these types of dermal fillers have an acceptable safety profile and lead to similar adverse events (see section 4.1).

In addition to dermal fillers, there are also other injectable treatments on the market such as autologous platelet-rich plasma (PRP) therapy and botulinum toxin (botox) injections. In PRP your own blood platelets are used to make your skin appear younger. Safety of this treatment is similar to that of dermal fillers, however botox injection does have some additional, less common side effects due to how it works (that is, blocking the facial nerves and cause muscle relaxation). All of the side effects disappear with time or when the treatment wears off.

6.1.2 Treatment of the skin surface

Treatments that are applied to the surface of the skin include agents such as retinoids, chemical peeling, and antioxidants. Of these, retinoids are currently considered the most effective, and there is evidence that retinoids can reverse fine wrinkling, sun spots, and improve skin elasticity. The most common adverse effects of retinoids are redness, scaling, dryness, and irritation, which usually reach maximum intensity within the first two weeks of application and diminish over time. Antioxidants such as vitamin C have also been shown to be effective in correcting wrinkles by reducing the breakdown of skin volume. However, antioxidants may not always penetrate the skin deep enough, so the effects observed may be less obvious. This treatment has the mildest complications of all skin surface agents, with skin flaking, redness and stinging being reported most commonly. Chemical peels using acids help correcting wrinkles by improving skin elasticity, volume and thickness.

Redness and flaking are again the most commonly observed side effects, although also increased skin sun sensitivity has been less commonly reported. The intensity of these side effects is dependent on the dose applied.

6.1.3 Energy-based devices

Examples of treatment that are energy-based include lasers, high frequency ultrasound (HFUS), radiofrequency (RF) devices, and fractional RF microneedling (FRFM) devices. All of these devices deliver heat to the skin, which leads to improvements in skin elasticity and wrinkles. The most common side effects of these devices are pain and bruising, or less commonly redness, swelling, tenderness and temporary tingling or itching sensations.

7 SUGGESTED TRAINING FOR USERS

The users/healthcare professionals received appropriate training on the conditions to safely use Hyaluronan Soft Tissue Filling Gel.

8 REVISION HISTORY OF SAFETY AND CLINICAL PERFORMANCE FOR PATIENTS OR LAY USERS

SSCP – Part 2 Revision Number	**Date issued**	**Description of change(s)**	**Revision validated by the Notified Body**
1.0	September 2024	New document	☒ No Validation language: English
2.0	March 2025	Update of the year when the first certificate was issued covering the device (section 1.4)	☐ Yes Validation language: English