SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

1. The identification of the device and the manufacturer, including the Basic UDI-DI and, if already issued, the SRN

TRADE NAME	Pbserum HA2.0
REFERENCE	PBS016.0 & PBW001.1CE
PRODUCT TYPE	Medical Device (injectable gel)
PRODUCT CLASSIFICATION	Class III, as per Rule 7 fourth section from Annex VIII Medical Device Regulation 2017/745
EMDN CODE	**M0406**, Post-operatory adhesion-prevention dressings
MDR CODE	MDN 1104 Non-active soft tissue and other implants, MDT 2011 Devices which require packaging, including labelling, MDS 1005 Devices in sterile condition, MDS 1008 Devices utilising materials or being wholly or mainly absorbed or locally dispersed in the human body.
UDI-DI – Basic UDI	843701973301_JHYALLA
UDI-DI	8437019733872 & 8437026968816
VARIATIONS	Two configurations of the *pbserum HA2.0* is marketed: - Pbserum HA2.0 Ref. PBS016.0 - WAID Injectable Ref. PBW001.1CE

The legal manufacturer of the product is:

PROTEOS BIOTECH, S.L.

Address: Polig. Industrial Romica, Calle Dublín, 58, 02007 Albacete

Mail: info@pbserum.com

Medical Devices Manufacturing License: 6422-PS

SRN: ESMF000000569

2. The intended purpose of the device and any indications, contraindications and target populations

HA2.0 is designed to be used as an anti-adhesive and anti-fibrotic treatment of patients with dermatological problems associated with fibrotic processes.

The excessive formation of fibrous scar tissue can give rise to a hypertrophic scar, which represents a form of pathological scarring.

HA 2.0 is a non-cross linked resorbable aqueous gel, destined to improve parameters such as vascularity, pigmentation, flexibility and the size of the hypertrophic scar. Being injected at the scar, HA 2.0 contributes to balance normal levels of intradermic HA in the extracellular matrix (ECM), improves the hydration and elasticity of the tissue due to its physicochemical characteristics and plays a fundamental role in tissue normalization and the correct formation of new fibrillar structures during the process of tissue repair.

HA2.0 acts favoring the tissue regeneration, through the action of hyaluronic acid in the debridement of fibrous scar tissue thanks to its anti-adherent properties.

HA2.0 acts as a moisturizing gel and physical barrier (anti-adhesion gel) which improves characteristic parameters of scars such as vascularization, pigmentation, thickness, elasticity, pain and pruritus.

Its use is exclusive by a health professional who can perform the injection technique in the area.

HA 2.0 is contraindicated in patients with hypersensitivity to any active ingredients or excipients and pregnant or breastfeeding women.

3. A description of the device, including a reference to previous generation(s) or variants if such exist, and a description of the differences, as well as, where relevant, a description of any accessories, other devices and products, which are intended to be used in combination with the device

HA 2.0 is a sterile, transparent viscoelastic gel supplied in 5 ml syringe packed in blister pack. It contains 2 ml of non-animal stabilized hyaluronic acid (HA).

The sodium hyaluronate is a widely used compound in intradermal injectables products already marketed and the water used as solvent fulfil the required parameter for being injected, so they do not present problems if used according to standard practice and following instructions for use. None of these ingredients is liable to result in tolerability concerns when administered via intradermal route in the concentrations and amounts included in soft-tissue implants.

None of the ingredients are manufactured from an animal or human source and it not incorporate any medicinal substance.

It is classified as a class III device under Rule 7 of Annex VIII of MDR 2017/745 since it is a surgically invasive device and it is for sort term use since it remains in the tissue for more than 1 hour but it totally absorbed before 30 days.

4. Information on any residual risks and any undesirable effects, warnings and precautions

Precautions

- HA2.0 is conditioned for one use per patient.
- Do not resterilize.
- Do not open the package before use and use immediately after opening.
- When using HA2.0, open in aseptic conditions.
- Do not use if the package is opened or damaged ori f the expiration date indicated on the package has been exceeded.
- HA2.0 should not be mixed with other products.
- Medical use.
- Do not ingest.
- Avoid contact with eyes and mucous.
- Use only with certified needles as a medical device.

Warnings

HA2.0 is only intended for use as an anti-adhesin gel for the debridement of fibrotic septa caused by internal injuries, wounds, surgeries and trauma of different origin. Confirm that the product has not expired and sterility has not been compromised before use. The product is only suitable for a single use, not reuse. In case of reuse, this can decrease the performance of the device and can cause a serious cross infection. The used syringes must be placed in a collector designed for this purpose or in a sharps container for this purpose or in a sharps container with biohazard risk.

Undesirable effects

In general, the product under study does not present adverse effects, although the injection in the affected area can be painful during the first and second applications for some patients. The day after the treatment, or after the first 5 hours of treatment, the patient may have a slight feeling of flu-like discomfort.

In some cases, due to the psychological-emotional state of the patient, the stress of being subjected to treatment or pain caused during treatment, the patient may suffer a vasovagal reaction syncope which may cause a sensation of weakness, hot flashes, vertigo, blurred vision, pallor sweating, hearing disorders, nausea, vomiting, diarrhea or fainting.

Patients should report inflammatory reactions that persist for more than a week or any other side effect with the product as soon as possible. The doctor should treat these effects appropiately. Any undesirable side effects associated with HA2.0 treatment should be reported to the distributor, manufacturer and/or to the following contact: +34 915 417 000 / info@pbserum.com

5. The summary of clinical evaluation as referred to in Annex XIV, and relevant information on post-market clinical follow-up

EFFICACY

DATA GENERATED WITH PBSERUM HA2.0

UNICENTRIC PILOT CLINICAL STUDY OF AN INJECTABLE MEDICAL DEVICE HA 2.0 FOR THE TREATMENT OF HYPERTHROPHIC SCARS

This study carried screened 55 patients, 40 of them completed the study and 39 were included in the statistical analysis.

The main parameter evaluation regarding performance was POSAS scale (Observer and patient), completed with Dermatological Life Quality Index (DLQI) and subject assessment survey. The main results obtained were the following:

- There is a significant decrease in observer POSAS scale from the start of the study, regarding its score on the first day (D0).

- There is a significant decrease in patient POSAS scale from the start of the study, regarding its score on the first day (D0).

- There is a significant reduction of the DLQI variable from the start of the study regarding the initial time (D0), with a p-value lower than 0.05.

Regarding the doctor opinion the 62% of them assessed the product as satisfactory for being recommended for the treatment of scars.

PERIODIC SAFETY UPDATE REPORT OF PBSERUM HA2.0

The clinical efficacy of the product has been demonstrated by means of the clinical trial carried out with pbserum HA2.0, with post-marketing studies of similar equivalent products of the same manufacturer, the evaluation of the literature of similar devices and confirmed by the positive valorization of physicians and patients in the post marketing surveys.

USABILITY REPORT OF PBSERUM HA2.0

This report, carried out previously to the launch of the product to the market confirmed that:

- There is not any use errors related with an inadequate labelling and/or IFU or with a misunderstand or no clear information of this labelling and/or IFU.
- Any adverse event or recall related with, the intentioned or not, re-use of the product have been detected, which implies that any additional risk elimination or reduction is needed for this task.
- The volume of the product to be applied in the fibrotic complication (scar) does not appear as a potential problem associated with the use of the device.

PMCF REPORT

Most professionals agree that the best results are obtained in the third session, confirming that the treatment recommended by the medical team of Proteos Biotech is adequate (3 intradermal injections located in the scar area spaced 15 days apart).

In addition, respondents were asked to rate the effectiveness of the PBSerum HA2.0 product on a scale of 0 to 5 on the various aspects of scar tissue improvement. The average rating was 4.0.

Considering the set of scores of 4 and 5, all features exceed 70% of responses, with the exception of pigmentation improvement, which still exceeds 50% of responses.

DATA GENERATED WITH OTHER EQUIVALENT DEVICES OF THE COMPANY

MULTICENTER CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF HYALURONIC ACID AND ENZYME COCKTAIL IN SCARS

This multicenter study published in the journal Cosmetic, Medical and Surgical Dermatology presents and evaluates the results of the treatment of the product pbserum HA1.5 that contains the same high molecular weight hyaluronic acid than in pbserum HA2.0 and a cocktail of recombinant enzymes collagenase pb220, Lipase pb500 and Liasa pb72k.

The study carried out on 42 patients who reported 44 scarring fibrosis was analyzed through a facultative assessment, following the Vancouver scale and the assessment of patient perception using the POSAS scale (Patient and Observer Scar Assessment Scale).

The treatment reveals a decrease in the irregularity of the scars in all cases from the first session. At the end of the study, a decrease in irregularity was observed in the

keloid group. The decrease in the irregularity of the scar was also significant in the case of hypertrophic scars.

PROSPECTIVE CLINICAL STUDY TO EVALUE THE CLINICAL REPONSE OF HYPERTROFIC SCARS TO THE USE OF HA1.5 HIGH

This clinical study carried out in Colombia used a very similar hyaluronic acid base product of PROTEOS Biotech, with the difference that it includes adjuvant enzymes (not included in pbserum HA2.0).

The study carried out on 20 patients who reported hypertrophic scars analyzed through a facultative assessment, following VANCOUVER and POSAS scales.

The treatment reveals a significant decrease in VANCOUVER scale from the 2nd visit.

Regarding each attribute of VANCOUVER (vascularity, height, pliability, and pigmentation) all of them showed a significant reduction at the end of the treatment.

Regarding POSAS scale from the point of view of the observer shows in all the categories except in pigmentation significant changes from the third visit.

Regarding POSAS scale from the point of view of the patient the statistical analysis shows that for the variables pain and pruritus are not observed significant changes during treatment, the variables color and firmness show significant changes from the third visit, and the thickness improves significantly from the second visit, and finally the irregularity in the scar improves from the third application of the treatment.

The results of the Dermatological Quality of Life Index (DLQI) were also positive.

DATA FOUND IN LITERATURE

Barrier antiadhesion effect of the HA: In vivo studies in humans

In human models, clinical studies confirm again reparative and antifibrotic effect of HA due to its anti-adhesion barrier function that prevents the proliferation of fibrosis, as shown following table.

Type of study and model used	Results
Randomized Controlled Trial (n = 21); Skin without epidermis by the Er-YAG laser in healthy volunteers	Laser wound was completely healed after 9 days in groups A and B, 12 days in group C and 16 days in group D; Healing is usually slow between days 1 and 6, faster after; The safety profiles of the treatments were favorable and comparable.
Cohort (n = 60); Partial thickness burns (average 3% of total body surface area);	On average, size of the wound was reduced by 50% on day 5; Complete epithelization in 93.3% of sample on day

Type of study and model used	Results
	21; Pain resolution in 91.7% of sample at day 10; No infections
Cohort (n = 40); persistent ulcers	Relevant reduction in ulcer size after 5 weeks in 80.0% of the sample, and slight or no improvement in 20.0% of the sample; Reduced pain in 50% of the sample, no pain in 40% of the sample and no change in pain intensity in 10% of the sample; Bacterial infection in wound exudates in 23.3% of the sample
Cohort (n = 30); Second-degree skin burns in the reepithelialization phase	Both agents are equally effective in reducing symptoms related to skin burns, such as erythema, tension, itching and burning sensation; Both agents led to a better overall appearance of the skin lesions; Ozonized oil prevented hyperpigmentation after the injury better than HA
Randomized Controlled Trial (n = 89); venous leg ulcers	Percentage of wound size reduction on day 45: 73 ± 4.6% in HA vs. 46 ± 9.6% in the control ($p = 0.011$); Number of healed ulcers: 31.1% in HA versus 9.3% in control on day 45 and 37.8% vs. 16.3% on day 60; Intensity of pain based on a lower visual analog scale in HA vs. control; A case of heart attack in the HA group and a death not related to the therapy
Randomized Controlled Test (n = 124); Pressure ulcers	Ulcer area reduction in all groups on day 36 (mean reduction of 48% compared to baseline) highest in all treatment groups vs. control; greater in 2 × PRGF + HA (average 80.4% vs. initial value); Complete healing of the wound: 32.0% in 2 × PRGF ($p < 0.002$) and in 37.5% 2 × PRGF + HA ($p < 0.004$); There are no infections until day 36
Randomized Controlled Trial (n = 34); Chronic periodontitis	Depth of sounding and number of cavities with depth of sounding ≥ 5 mm reduced in both groups; Superior in test vs. control in months 3 and 6; Reduction in the count of Treponema denticola and Campylobacter rectus; Superior in test vs. control
Case series (n = 5); wound dehiscence and tendon exposure after the removal of Morton's neuroma surgery	Complete healing of the wound on day 30; Walking recovered after an average of 2 weeks; There are no side events
Retrospective study (n = 29); Patients with removal of basal cell carcinoma of the face	Re-epithelialization progressively occurred from the periphery to the center of the wound
Surgical wounds in (n = 44) patients of surgeries for the sinusitis treatment.	The adherence rate was the highest at 2 weeks after the operation and was significantly lower in the group treated with HA-CMC than in the control on all postoperative days.
Retrospective observational study of gynaecological surgical wounds (n = 125) from laparoscopic surgery	50% of the patients ($p < 0.005$) with chronic pelvic pain had thick fibrous adhesions. HyaCorp reduces total and subtotal laparoscopic hysterectomies (LTH, LSH), myomectomies and endometriosis.

Type of study and model used	Results
Retrospective analysis of 155 patients treated for skin rejuvenation, age-related laxity and rhytidosis, hypertrophic and acne scars and striae	Patients were highly-satisfied with the treatment results in all categories with the average satisfaction scores of 3.68 (NCL-HA) and 3.76 (CL-HA). Low incidence of side effects including bruises (7%) and temporary local edema (1%)

For further details, the main results of other human clinical trials carried out with approved injectable medical devices for aesthetic purposes, but used in the field of scar management are described:

FACIAL INJECTIONS OF HYALURONIC ACID-BASED FILLERS FOR MALFORMATIONS. PRELIMINARY STUDY REGARDING SCAR TISSUE IMPROVEMENT AND COSMETIC BETTERMENT

This study evaluates effects on softness and elasticity as a secondary effect, following injection in patients presenting with congenital or acquired facial malformations.

46 sessions of injections in 32 patients, aged from 13–32 were performed.

Results: Cross-linked hyaluronic acid-based fillers offered very subtle cosmetic results and supplemented surgery with a very high level of satisfaction of the patients. When injected in fibrosis, the first session enhanced softness and elasticity; the second session enhanced the volume. Cross-linked hyaluronic acid-based fillers fill sunken areas and better softness and elasticity of scar tissues.

MANAGING PATHOLOGIC SCARS BY INJECTING AUTO-CROSS-LINKED HYALURONIC ACID: A PRELIMINARY PROSPECTIVE CLINICAL STUDY

This pilot study aims to preliminarily investigate whether auto-cross-linked hyaluronic acid (HA) may also be effective in treating pathological scars resulting from burns, trauma or iatrogenic causes.

Results: Forty-one patients were recruited. No significant adverse event was observed. At T90, the median observer total score and the median patient total score decreased. The difference was significant ($p < 0.001$) in both cases. Traumatic injuries and young patient's age were the most significant predictors of a positive treatment outcome.

A SPLIT-FACE, BLIND, RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL INVESTIGATING THE EFFICACY AND SAFETY OF HYALURONIC ACID FILLER FOR THE CORRECTION OF ATROPHIC FACIAL SCARS

This study aims to analyze the efficacy and safety of a hyaluronic acid filler for atrophic facial scars.

Results: According to the blind evaluator, there was a significant reduction 90 days after the last treatment.

DUAL-PLANE HYALURONIC ACID TREATMENT FOR ATROPHIC ACNE SCARS

This study aimed to treat atrophic acne scars using the injection of hyaluronic acid.

Results: A total of 8 out of the 12 patients reported moderate improvement, two indicated marked improvement and two rated minimal improvement. Dermatologists' mean global evaluation score was significant and meant improvement in patients' skin. The treatment led to impressive improvement in the depth of the scars.

SAFETY

DATA GENERATED WITH PBSERUM HA2.0

UNICENTRIC PILOT CLINICAL STUDY OF AN INJECTABLE MEDICAL DEVICE HA 2.0 FOR THE TREATMENT OF HYPERTHROPHIC SCARS

- No serious adverse events have occurred.
- Adverse Events of related or probable causality have been recorded in 6 of the 48 subjects included.
- 2 of the 48 subjects were dropped out of the study by AE.
- Itching is the most frequent AE associated with IP.
- The severity of the AEs was generally moderate.
- The causality of the AEs was generally probable.

As indicated in the Patient Information Consent, the injection, due to the type of fibrotic tissue to be treated, is painful for most patients. As it is an intrinsic and expected AE of the type of procedure and not of the product itself, it was not considered as a related AE in this trial, except for pain that was long-lasting or at least moderate, or that resulted in the dropout of the study even if it was mild.

PERIODIC SAFETY UPDATE REPORT OF PBSERUM HA2.0

This report confirmed the absence of recall or client complains and the valorization of physicians and patients regarding efficacy and safety of the product. In this PSUR, apart from the pre-market clinical trial and the evaluation of recall or adverse events, post-market clinical activities have been carried out for the treatment of the scars and a review of literature.

USABILITY REPORT OF PBSERUM HA2.0

This usability report does not detect any risk that could threaten the security of the product, nor related with the labelling/IFU, re-use, volume of the product, or even, with the volume of the product to be applied. Any adverse event was detected.

PMCF REPORT

A series of questions are posed according to the PMCF plan, analyzing which adverse events have been observed by clients and with what frequency.

It is observed that in general the percentage of clients who have not observed the adverse events specified in the survey is in the majority and even exceeds 70%.

Among the list of adverse events identified, the most common (with a score of less than 70%) were:

- Pain at the injection site
- Erythema at the injection site
- Urticaria or rash
- Edema

Pain, erythema, erythema, urticaria or localized and transient edema are not serious symptoms expected due to any injectable.

The only observable symptoms whose frequency exceeds 15 patients per year are the aforementioned “pain at the puncture site” and “erythema at the puncture site”, common symptoms associated with the method of action of the product.

Analyzing the persistence of these events, the majority disappeared after 48h.

DATA GENERATED WITH OTHER EQUIVALENT DEVICES OF THE COMPANY

MULTICENTER CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF HYALURONIC ACID AND ENZYME COCKTAIL IN SCARS

The safety results of this study indicated that the product is safe, and no severe adverse effects (AE) were observed in any case. All reported adverse effects were mild, as well as normal events in the injections applied in scar fibrosis. By the type of AE, the most observed was pain, possibly due to the excessive maturity of the scar fibrosis.

DATA FOUND IN LITERATURE

Although for the evaluation of the efficacy of the product, literature publication for in vitro and ex vivo (animals) models has been compiled, for the safety of the products, only the publications of in human models has been selected, to detect any security risk when using similar products in humans.

- Juhász I., et al. 2012

No obvious infectious complications or adverse events were observed during the whole study.

- Onesti MG, et al. 2013.

This study concludes that the use of the product in peri wound skin presents no collateral effect and contraindications.

- Campati A, et al. 2013

None of the patients involved in the trial developed mild or severe side effects; thus, all completed the study.

- Erick S, et al 2013.

No adverse effects of HA were observed during the study in the years 2007 and 2008

- De Angelis, et al. 2013

No patients had complications as wound infections, edema, persisting pain or wound dehiscence.

- MacGuillis, et al. 2021

Low incidence of side effects including bruises (7%) and temporary local edema (1%). minimal downtime, pain or side-effects

- Abdelwahab AA, et al. 2022

No serious side effects were detected in the study, being edema, pain, and erythema detected after treatment were which lasted for 3–10 days in most patients.

- Siperstein R, et al. 2022

This study reported as safe to treat acne scars, although mild transient pain was reported by most patients.

BENEFIT/RISK PROFILE

Scar fibrosis often represent a significant medical and cosmetic problem. The symptoms that significantly affect the quality of life and the personal image of the individuals who suffer from them are: itching, pain and the poor aesthetic appearance that these types of scars produce, so the benefit/risk balance is acceptable, since the erythema, edema, bruising and redness that could appear associated to the injection sites is tolerable and will disappear in less than 72.

The benefits for the patients are meaningful and measurable in terms of scar improvement, increasing softness, elasticity and volume of the scaring tissue, preventing adhesion, promoting the dermis re-epithelization, etc.

Concerning the risk associated to the use of the device, the evaluation of the adverse events or side-effects in the clinical evaluation of similar devices and with HA2.0 has demonstrated that no serious events or incidents has arisen. The percentage of effects reported was very low and most of these effects were tolerable.

Moreover, most of the HA evaluated in literature are cross-linked ones, which is the main responsible of possible side effects. Therefore, HA2.0 which is a non-crosslinked HA is less likely to induce any serious event.

Therefore, taking into account the population who may benefit using the product, clinical parameters that are improved, the probability of experiencing improvement in these clinical parameters and the speed of treatment, comparing it with the risk associated with the use of the product, the evaluation of adverse effects in the literature, and being these similar to other HA found on the market, it has been demonstrated that they are tolerable adverse effects and that the benefit/risk balance is acceptable.

6. Possible diagnostic or therapeutic alternatives

Multiple treatment alternatives have been used for fibrotic scars, all with varying degrees of success. Among the treatment modalities that can be used are silicone gels, compression therapy, surgical excision followed by radiotherapy, applications of intralesional steroids, cryotherapy, therapy with different types of lasers, intralesional bleomycin, among others.

Among the treatments for intralesional application, corticosteroids are the most commonly used in fibrotic scars. The reports regarding its effectiveness are variable, with reports ranging from 50% to 100% and with recurrences between 9 and 50% according to various studies. The application is painful and may cause skin atrophy, telangiectasia, necrosis or ulceration.

The simple surgical excision of scars is associated with recurrence rates ranging from 45 to 100%, so it is an alternative that is in disuse as monotherapy.

Radiatiotherapy causes death and early senescence of fibroblasts in abnormal scars. This has a recurrence rate of 0 to 20%, however, radiation exposure has important adverse effects (carcinogenesis, radiation to other structures close to or deep to the scar) and contraindications that must be assessed in each specific case.

The use of compression therapy or pressotherapy is effective in young fibrotic scars and to prevent recurrences after surgical excision. In a study of 88 scars in the auricle treated by surgical resection with subsequent pressotherapy, they had a recurrence rate of 30%.

Silicone gels are also used, with described effectiveness around 60%, manifested as a decrease in the thickness and colour of the scar. Its greatest use is when it is used in recent scars.

Cryotherapy with liquid nitrogen has been used as monotherapy and as a complement to intralesional corticosteroid therapy, with variable results. The success rates vary between 51 and 80%. This type of treatment is limited throughout the treatment cycles by the multiple monthly sessions required, as well as by the common adverse effects such as pain, blistering and hyper- or residual hypopigmentation.

5-Fluorouracil (5-FU) can also be used intralesional. In scars, it acts by inhibiting the proliferation of fibroblasts. Response rates in some studies vary from 70-80%, with relapse rates around 50%.

Bleomycin has been used in some studies for the treatment of fibrotic scars in which scars have been reduced by 36-66% with recurrence rates that vary around 15%. Like 5-FU, bleomycin has important adverse effects, mainly causing ulceration of the scar with pain.

Tension is considered an important factor in the genesis and maintenance of fibrotic scars. The application of botulinum toxin reduces the tension in the scars. The percentages of effectiveness vary around 40%. This treatment option is expensive because of the frequency of application for a long period of time.

7. Suggested profile and training for users

Pbserum HA2.0 is aimed at physicians from different specialties, but more specifically at:

- Plastic surgeons.
- Dermatologists.

- Aesthetic doctors.

The training plan for users of pbserum HA2.0 follows these steps:

1. Full review of Pbserum's *professionals* website.
2. Kick off one-to-one with Medical Affairs team.
3. Before and after clinical cases presentation.
4. Certification and ready to use.

8. Reference to any harmonised standards and CS applied

PROTEOS is citing compliance with the following standards:

- ISO 10993-1:2018. Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.
- ISO 10993-2:2022. Biological evaluation of medical devices – Part 2: Animal welfare requirements
- ISO 10993-3:2014. Biological evaluation of medical devices. Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-5:2009. Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity
- ISO 10993-10:2021. Biological evaluation of medical devices – Part 10: Tests for skin sensitization
- ISO 10993-11:2017. Biological evaluation of medical devices – Part 11: Tests for systemic toxicity
- ISO 10993-12:2021. Biological evaluation of medical devices – Part 12: Sample preparation and reference materials
- ISO 10993-17:2023 Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents
- ISO 10993-23:2021. Biological evaluation of medical devices - Part 23: Tests for irritation
- ISO 14155:2020. Clinical investigation of medical devices for human subjects - Good clinical practice.
- ISO 14971:2019. Medical Devices. Application of risk management to medical devices.
- ISO 15223-1: 2021. Medical Devices – Symbols to be used with medical device labels, labeling and information to be supplied – Part 1: General requirements.
- ISO 20417:2021. Medical devices - Information to be supplied by the manufacturer
- ISO 11607-1:2019. Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems

- ISO 11607-2:2019. Packaging for terminally sterilized medical devices. Part 2: Validation requirements for forming, sealing and assembly processes.
- ISO 11737-1:2018. Sterilization of health care products - Microbiological methods Part 1: Determination of a population of microorganisms on products
- ISO 13408-1:2015. Aseptic processing of health care products - Part 1: General requirements.
- ISO 13408-2:2018. Aseptic processing of health care products - Part 2: Sterilizing filtration
- ISO 22248:1992. Packaging. Complete, Filled Transport Packages. Vertical Impact Test by Dropping
- ISO 14644-1:2015. Cleanrooms and associated controlled environments. Part 1: Classification of air cleanliness by particle concentration.
- 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 14644-4:2022. Cleanrooms and associated controlled environments. Part 4: Design, construction and start-up.
- ISO 14644-5:2004. Cleanrooms and associated controlled environments. Part 5: Operations.
- ISO 14698-1:2003. Cleanrooms and associated controlled environments. Biocontamination control. Part 1: General principles and methods.
- ISO 14698-2:2003. Cleanrooms and associated controlled environments. Biocontamination control. Part 2: Evaluation and interpretation of biocontamination data.
- 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 15883-1:2006. Washer-disinfectors - Part 1: General requirements, terms and definitions and tests
- ISO 15883-2:2006. Washer-disinfectors - Part 2: Requirements and tests for washer-disinfectors employing thermal disinfection for surgical instruments, anesthetic equipment, bowls, dishes, receivers, utensils, glassware, etc.
- ISO 7730:2005. Ergonomics of the thermal environment - Analytical determination and interpretation of thermal comfort using calculation of the PMV and PPD indices and local thermal comfort criteria.
- ISO 19011:2018. Guidelines for auditing management systems
- EN 62366-1:2015. Medical devices - Part 1: Application of usability engineering to medical devices
- ICH Guidance for Industry. Q9 Quality Risk Management
- ASTM F838. Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration
- ASTM F1980 – 02. Standard Guide for Accelerated Aging of Sterile Medical Device Packages

- ASTM D5276-19. Standard Test Method for Drop Test of Loaded Containers by Free Fall

PROTEOS would like to declare that the Quality Management System (QMS) of the organization follows ISO 13485:2016 standard certified by the notified body KIWA Certification Services.

In addition, the following guidelines have been used and/or applicable either for the product under the scope of current Technical File, and/or procedures related to the QMS:

- MDCG 2019-5 Registration of legacy devices in EUDAMED
- MDCG 2019-9 Summary of safety and clinical performance
- MDCG 2020-3 Guidance on significant changes regarding the transitional provision under Article 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD
- MDCG 2020-5 Clinical Evaluation - Equivalence A guide for manufacturers and notified bodies
- MDGC 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
- MDGC 2020-13 Clinical evaluation assessment report template
- MDGC 2020-15 MDCG Position Paper on the use of the EUDAMED actor registration module and of the Single Registration Number (SRN) in the Member States
- MDGC 2021-5 Guidance on standardization for medical devices
- MDGC 2021-25 Application of MDR requirements to "legacy devices" and to devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC
- MDCG 2022-21 Guidance on periodic safety update report (PSUR) according to regulation (EU) 2017/745 (MDR)

9. Revision history

Document	Version	Date
Summary of safety and clinical performance	1.0	18/11/2024