Summary of Safety and Clinical Performance

Lyoplant®

Further information are in the work instruction 4-1-11-512-0 Instructions for Summary of Safety and Clinical Performance

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List of abbreviation / glossary

Basic UDI-DI	Basic Unique device identification device identifier
CAPA	Corrective and preventive action
CE	Conformité Européenne
CSF	Cerebrospinal fluid
FSCA	Field safety corrective action
FSN	Field safety notice
SSCP	Summary of Safety and Clinical Performance
SRN	Manufacturer's single registration number
NB	Notified Body
MDR	Medical Device Regulation
BSE	Bovine Spongiform Encephalopathy
PMCF	Post-market Clinical Follow-up
MRI	Magnetic Resonance Imaging
CCOS	Chicago Chiari Outcome Scale
DIN	Deutsches Institut für Normung (English: German Institute for Standardization)
EN	European Norm
ISO	International Organization for Standardization
TSE	Transmissible Spongiform Encephalopathy

Part 1: Intended for 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 the device.

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

The following information is intended for users/healthcare professionals.

1 Device identification and general information

1.1 Device trade name(s)

Lyoplant®

Table 1: Delivery forms and packaging sizes

REF	DIM	Box content
1066021	LYOPLANT 6 cm x 14 cm	1 piece
1066030	LYOPLANT 8 cm x 9 cm	1 piece
1066048	LYOPLANT 4 cm x 10 cm	1 piece
1066050	LYOPLANT 5 cm x 6 cm	1 piece
1066064	LYOPLANT 4 cm x 5 cm	2 pieces
1066080	LYOPLANT 2 cm x 10 cm	2 pieces
1066102	LYOPLANT 1.5 cm x 3 cm	2 pieces
1066242	LYOPLANT 6 cm x 8 cm	1 piece

1.2 Manufacturer's name and address

Aesculap AG

Am Aesculap-Platz

78532 Tuttlingen/Germany

1.3 Manufacturer's single registration number (SRN)

Manufacturer's single registration number: DE-MF-000005504

1.4 Basic UDI-DI

Basic UDI-DI for Lyoplant®: 403923900000150529

1.5 Medical device nomenclature description / text

P900402 Biodegradable devices, filler and reconstructive

1.6 Class of device

Classification according to MDR according to Annex VIII: Class III device

- Rule 8.3 (resorbable implant)
- Rule 18 (manufactured utilizing tissues of animal origin)

It is a medical device because the product and the described intended use correspond to the definition of a medical device of the MDR according to Art 2 (1).

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

Lyoplant® is CE-certified since 1997.

1.8 Authorized representative if applicable, name and the SRN

Not applicable.

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

TÜV SÜD Product Service GmbH

Ridlerstraße 65

80339 München

Single identification number: 0123

2 Intended use of the device

2.1 Intended purpose

Lyoplant® is an implant of purified collagen obtained from bovine pericardium. It is intended to be used as a dura mater substitute in neurosurgery.

2.2 Indication(s) and target population(s)

Replacement and extension of connective tissue structure in neurosurgery:

- For covering cerebral and cerebellar dura defects
- For cerebral decompression surgery when there is elevated intracranial pressure
- For covering spinal dura defects
- For spinal decompression surgery

There is no restriction regarding the intended patient population additional to the indications and contra-indications.

2.3 Absolute contraindications

Lyoplant® should not be applied:

- In infected regions
- To replace connective tissue structures that are subject to mechanical stress
- In case of known hypersensitivity against proteins of bovine origin

2.4 Relative contraindications

The following conditions, individual or combined, can lead to delayed healing or compromise the success of the operation:

- Medical or surgical conditions (e.g., comorbidities) which could hinder the success of the operation.

In the presence of relative contraindications, the user decides individually regarding the use of the product.

3 Device description

3.1 Description of the device

Lyoplant® is a pure collagen implant obtained from bovine pericardium. The membrane is used for the replacement and extension of connective tissue structures in neurosurgery (Figure 1). The lyophilization (freeze-drying) process guarantees that Lyoplant® retains its loose fibrous structure to offer appropriate conditions for integration after implantation. After implantation, the colonization of the implant by connective tissue cells begins after only a few days. The collagen will be converted into human connective tissue. The complete revitalization takes place within a period of one to three months.

Figure 1: Product image of Lyoplant® (left) and material structure of Lyoplant® (right)

Thickness of Lyoplant® is dependent on structure of the native pericardium and is variable, typical values are in the range of 0.8 mm ± 0.2 mm. Due the irregular structure, the weight per unit area is specified to 100 -180 g/m². The overall porosity of Lyoplant is 66 ± 3%.

Lyoplant® belongs to the neurosurgical implants.

- During the intended use the following organs/tissue/body fluids come in contact with the device: brain, spinal cord, bone, dura mater, cerebrospinal fluid as well as blood.
- The devices are necessarily used together with non-absorbable sutures.
- The application of the devices is invasive.
- The application period of the devices is long-term.
- The devices are intended for clinical users: Surgeons with required knowledge about the surgical technique and surgical training who are aware about the in vivo characteristics of the product, operating room personnel (set-up, handling, functional check).

- Lyoplant® implants are for single use and are shipped in a sterile way. They will be sterilized by ethylene oxide.
- The devices do not contain pharmaceutical components or human tissue; they are neither blood products nor radioactive.

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

Since the CE-certification of Lyoplant® in 1997, neither the final product specifications of Lyoplant® have been further developed nor changed in terms of its product characteristics. No variants of Lyoplant® other than the different product and packaging sizes (see 1.1) are available.

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

Lyoplant® must be sutured with nonabsorbable suture material and can be additionally fixed with fibrin glue.

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

There are no other devices and products which are intended to be used in combination with the device.

4 Risks and warnings

4.1 Residual risks and undesirable effects

Potential complications that the manufacturer is currently aware of:

- Infection
- Cerebrospinal fluid leakage
- Adhesion
- Allergic reactions to proteins of bovine origin

According to the product-related literature of Lyoplant® that were identified in the Clinical Evaluation Report, CSF leaks are a common complication with incidence rates from 0.0 % to 7.5%. Furthermore, incidence rates from 0.0% to 3.8% for infections have been reported (1).

Foreign body reactions such as allergic reactions due to material incompatibilities or adhesions to the surrounding tissue were not reported for Lyoplant® within clinical investigations with a prospective or retrospective study design and with higher sample sizes. However, a case report described a rare foreign body reaction (2). In this case report, the authors described the foreign body reaction as a rare complication which could be confirmed by the market data analysis of Lyoplant®. In comparison to the state of the art, CSF leaks are a common complication, regardless of the type of dural closure (incidence rates from

5.13% to 29.6%). Furthermore, incidence rates from 5.64% to 16.0% for infections were identified within the state of the art. Regarding the occurrence of adhesion and foreign body reactions, occurrence rates of 10.78% and up to 6.5% respectively were reported.

4.2 Warnings and precautions

- Lyoplant® should not be used after the expiry date given.
- Lyoplant® should be used immediately once the package is opened.
- Lyoplant® should be stored at 25 ± 5 °C.
- Lyoplant® may only be used if the packaging is undamaged. Opened packs of Lyoplant® and pieces of implant that are no longer required, must not be used later.
- Lyoplant® may not be resterilized! Resterilization must not be carried out, because the structure of the Lyoplant® implant and, hence, its behaviour in vivo can be detrimentally affected.
- Safety regarding the transmission of zoo-anthroponoses

  Since bovine material from New Zealand is regarded as safe by the European authorities with respect to BSE (bovine spongiform encephalopathy), the raw material is imported from there. Furthermore, Lyoplant® is subjected to treatment with NaOH during processing, to further reduce any theoretical risk, by means of this recognized decontamination method.

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

No Field Safety Notices (FNS), Field Safety and Corrective Actions (FSCA), recalls or Corrective and Preventive Actions (CAPA) were necessary for the products since its introduction in the market.

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

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

As part of the market approval, a comparative clinical study was conducted by B.Braun Melsungen AG in which Lyoplant® was compared with Lyodura®. In this study, 120 patients, 90 of whom completed the study as planned, were observed over a postoperative period of twelve months. The aim of the study was to evaluate the occurrence of complications and the handling characteristics of the dura substitute materials used. The result of the study was that Lyoplant® achieved comparable results regarding the complication rate but showed significantly better handling properties. Three complications were observed intraoperatively. Two patients treated with Lyoplant® suffered from cerebral swelling and dura laceration,

respectively. One hemorrhage was recorded during the treatment with Lyodura®. During the inpatient stay 14 complications were observed postoperatively. One infection was observed in the Lyoplant® group and one in the Lyodura® group. Further complications were hematoma (Lyoplant: n=3; Lyodura®: n=1), cerebral swelling (Lyodura®), and other complications (Lyoplant®: n=4; Lyodura®: n=5) such as bronchitis or liquor fistulae. Between the time of hospital discharge and follow-up (12 months postoperatively), additional complications were observed in four patients, with Lyoplant® patients suffering an infection and a cerebral infarction. Adverse events were not related to the use of Lyoplant® itself.
CSF tightness as well as suture tear resistance was present in the Lyoplant® group in all cases. Lyodura® also proved to be CSF-tight, but in two patients the suture tore out. Regarding handling, the surgeons rated Lyoplant as follows (Table 2):

Table 2: Evaluation of the usability during the clinical study

	Good	Fair	Bad
Ability to cut	100.0%	0.0%	0.0%
Thickness	91.7%	8.3%	0.0%
Stiffness	98.3%	1.7%	0.0%
Adaptability	100.00%	0.0%	0.0%
Ability to suture	95.0%	5.0%	0.0%

5.3 Summary of clinical data from other sources, if applicable

User survey

Customer survey – results

In total, eleven customers of different clinical institutions from Germany, Italy, and South Korea have been taken part in this user survey. Most of the participants can be considered as experienced in the use of Lyoplant®. Two of the respondents have been using Lyoplant® for between 3 to 5 and 5 to 10 years respectively. Four users have even been using Lyoplant® for longer than 10 years. Two surgeons had been using Lyoplant® for less than 12 months at the time of the survey and one user had between one and three years of experience. Almost half of the respondents reported using Lyoplant® more than 100 times per year followed by up to 10 applications per year by three users (27.27%). One user each reported performing between 11 to 20, 21 to 50 and 51 to 100 procedures per year with Lyoplant®.

The questionnaire included clinical aspects (such as the specification of indications, observed complications) as well as performance aspects (e. g. handling properties). The analysis of the results of the user survey focuses on the usability of Lyoplant® in terms of overall satisfaction, the ability to cut, ability to suture, adaption behavior to anatomical structures, tensile strength, suture retention strength, and liquid tightness. The analysis of the questionnaire has shown a positive outcome regarding the use of Lyoplant®.

The main result of the survey is a positive evaluation of the general use of Lyoplant®. More than a quarter of respondents rated the application as excellent (27.27%). Almost half of the respondents rated the handling as very good (45.45%) and 27.27% of the participants rated the application as good.

Regarding the cutting ability of Lyoplant®, most of respondents were very satisfied with the material properties. Thus, five users (45.45%) each rated the cutting ability as excellent or very good (45.45 %). Another operator (9.09%) rated the cutting ability as good.

Regarding the sewability of Lyoplant®, the majority of respondents were very satisfied with the material properties. Four users (36.36%) rated the suturability as excellent; five as very good (45.45 %). Two more operators (18.18%) rated the cutting ability as good.

The adaptability of Lyoplant® to anatomical structures was predominantly rated satisfactory. Three users (27.27%) rated the moldability as excellent, two users (18.18 %) as very good and five (45.45%) as good. One user (9.09%) rated the adaptability as poor but did not provide any further information regarding the causes. The explanation here could be the difficult anatomical localization. The data refer to the application in neurosurgery, where, for example, less space is available for applying Lyoplant® in the area of spinal dural defect coverage. User experience could also play a role. Of the eleven participants in the user survey are two surgeons (18.18%) who have only been using Lyoplant® for less than one year. A total of three users (27.27%) applying Lyoplant® up to ten times per year, while five users (45.45%) perform more than 100 procedures per year with Lyoplant®. Accordingly, the poor adaptation to anatomical structures could also be attributed to a learning curve that has not yet been fully completed or can be explained by short rehydration time of the Lyoplant®.
Liquid tight closure was evaluated acceptable. Nine users rated the liquid tightness at least as good (36.36%), very good (18.18%), or as excellent 27.27%). In addition, two users rated the liquid tightness as fair (18.18%). None of the users have made negative experiences reaching a liquid tight closure by using Lyoplant®.

The tensile strength of Lyoplant® was also rated satisfactorily. More than three quarters of the respondents rated the tear resistance as excellent (27.27%) or very good (54.55%). Two other users rated the tear resistance as good.
The tear-out strength of the suture was predominantly rated satisfactory. Four users (36.36%) rated the suture retention strength as excellent, five as very good. One user each (9.09%) rated it as good or fair.

Furthermore, the results of the user survey have shown that the surgeons are using fibrin glue as an additional sealing. Six users gave feedback that they always using fibrin glue, whereas two surgeons using fibrin glue often.

Expert Report

In addition, an experience report by the University Hospital of Trondheim confirms the clinical outcome of Lyoplant® as a dura substitute (Application and Tolerance Report). Between February 1994 and November 1994, a total of 33 patients underwent neurosurgical interventions (e. g. meningiomas, adenomas of the pituitary, malformations) which required the use of Lyoplant®. Regarding its suppleness, sewability, seam tearing, modelability, cutability Lyoplant® was rated at least comparable or better compared to the previously known materials and a liquid-tight closure was possible in all cases. Neither in the early postoperative period (during the hospital stay) nor within the long-term follow-up period (1 to 9 months) no

complications related to the application of Lyoplant® have been observed. No foreign body reaction was present. Detailed information can be found in the Application and Tolerance Report.

Literature on the product

In a randomized, controlled clinical trial, LAUN et al. compared the use of Lyodura® and Lyoplant in 102 patients (51 per group) regarding their intraoperative handling, wound healing properties, and the occurrence of intra- and postoperative complications. Mean size of the implants used was 14cm² and mean duration of surgery was similar in both groups (5 hours). Application of the implants in both groups was comparable: cutting the implants to the required size and were fixated by running sutures. Fibrin glue was used in 47% of the cases as an additional sealant. The surgeons assessed the handling properties of Lyoplant® superior to Lyodura® in 98% of the cases compared to Lyodura® which was judged to be too stiff in 96%. Furthermore, Lyodura® was rated to have an inconvenient thickness compared to Lyoplant® (20% vs. 0%). In addition, compared to the Lyoplant® group the required rehydration time was to slow in the Lyodura® group. In terms of cutting behaviour, suturability, and watertightness both implant types have been judged as equal. Occurrence of intraoperative complications were comparable in both groups. In the Lyoplant® group six complications have been observed postoperatively: infection = 1, hematoma = 1, septic complication =1, brain edema = 2, thrombosis =1 which was slightly higher compared to the Lyodura® group in which three complications occurred (infection, brain edema, thrombosis). None of the observed complications were related to the application of Lyoplant® or Lyodura®. (3)

In cases of reoperation, for example due to recurrent tumours, biopsies of Lyoplant® implants were taken (n=9) postoperatively between 4 days to 24 months. The biopsy four days postoperatively, has shown the beginning of infiltration of fibroblasts and histiocytes into the implant, which is possible, due to its natural open porous structure. After three months, an implant sample was found to be reduced in its thickness by one half. Polarization microscopy revealed newly formed delicate collagenous fibrils which firmly connect remnants of the graft material with the inner and outer neomembranes. Eleven months status after initial surgery has shown a consisted portion of well-preserved collagenous fibers which was entirely revitalized. After two years only a small layer of the implant, approximately reduced to a tenth, was present. The authors described the implant incorporation as excellent and the transitional zone as well vascularized. (3)

In their retrospective analysis, LITVACK et al. compared two types of commercially available collagen sponges (monolayer vs. bilayer sponges) with respect to the incidence of CSF leakage and infection in a total of 475 patients. Lyoplant® was used in 38 cases together with monolayer collagen (DuraGen or DuraGen Plus). Complications included CSF leakage (fistulas and clinically diagnosed pseudomeningocele) and infections (wound infections, abscesses, and meningitis). The overall rate of postoperative CSF leakage was 6.7% (32 of 457, including 23 fistulas and 9 pseudomeningocele). The postoperative infection rate was 4.2% (20 of 475), 14 of which were superficial wound infections and 6 deep (meningitis or abscesses). The most common infectious agents were S. aureus with 55% of cases and MRSA with 15%, 20% were culture negative. While the CSF leakage rate was lower in the Bilayer group (5.5% vs. 7.5%), the infectious rate was higher there (4.9% vs. 3.8%), but both differences were not statistically significant. The use of

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Lyoplant® showed no significant influence on the leakage or infection rate. The differences in clinical outcome between the mono- and bilayer sponges were not significant. Because the products applied were staggered in time, the observed nonsignificant differences could be due in part to other time-dependent effects. The rate of deep infections was 1.3% with 6 of 457 cases, with fewer total infections in the Lyoplant® group. Thus, the use of Lyoplant® in combination with monolayer sponges does not indicate any efficacy or safety issues. (1)

In another case-report, a full-term newborn boy presented with a large full thickness calvarial skin and skull defect in the vertex over the superior sagittal sinus, posterior to the coronal. In the repair of congenital absence of part of the skin, bony skullcap, and dura mater, Lyoplant was used to close the dural gap in the region of the superior sagittal sinus. In addition, the "scalp rotational flap" technique was used for skin coverage, and the pediatric patient received a helmet for mechanical protection.

One year after surgery, complete skin closure and partial bone closure were achieved. Cranioplasty was scheduled for a later date. Postoperative period was uneventful, except for the distal part of the flap, and it was managed by routine wet dressing until it was closed by formation of granulation tissue and epithelization. (4)

The authors discuss in detail the choice of Lyoplant® as a dura substitute and consider the extracellular bovine pericardial matrix as a suitable acellular resorbable scaffold for tissue regeneration. Since the material is avascular, hyperacute rejection reactions involving endothelial activation and intravascular thrombosis are avoided. Extracellular matrix-based biomaterials used as xenografts induce an immune response primarily of the TH2 type, which is more comparable to remodeling than to rejection. GAZIOGLU et al. describe a case of successful application of Lyoplant® in its claimed indication, describe its properties, and provide a detailed rationale for the choice of this material for dura replacement in pediatric neurosurgery. (4)

In two cases (male, 16 and 18 years, respectively, with severe skull base fractures), KIM et al. described their experience using the pedicled nasoseptal flap in the complicated basal skull fracture treatment. The authors describe the indication area of skull base fractures as follows: Skull base fractures occur in 3.5-24% of skull fractures. CSF loss occurs in 5-11% of skull base fractures and is independent of severity. Posttraumatic CSF from the nose resolves spontaneously within a week in about 85% of cases but recurs in about 7% of cases. Meningitis represents the most important complication in CSF leak patients. The incidence here is about 30% in acute leakage and 57% in chronic leakage. Mortality from meningitis in traumatic CSF leakage reaches 10% after traffic accidents and CSF edema from the nose due to dura injury Here, the use of Lyoplant® to close an accidental dura tear with leakage during surgical reconstruction of the skull base is described in one case. Case 2 also describes duraplasty for multiple tears and massive CSF loss, but the material used is not specified. Both cases described were healed after 12 and 10 months, respectively, with no evidence of CSF loss. The result demonstrates the successful use of Lyoplant in the claimed indication in at least one case. (5)

PAZKABAN conducted a feasibility study to evaluate the safety and performance of a minimally invasive approach for the treatment of Chiari type I malformations. Lyoplant® was implanted as a dura substitute in six patients as part of the duraplasty procedure to be performed in this study. In principle, the minimally invasive approach was successfully implemented in all patients. In none of the procedures it was necessary to switch to the conventional open approach. Furthermore, neither intraoperative complications nor deterioration of the neurological condition occurred during the postoperative follow-up. Complete recovery of symptoms indicated in the preoperative period was noted in three patients after completion (CCOS score of 16 points), while mild symptomatology was still noted in another three patients (mild neck pain, mild headache, mild numbness, and awkwardness in left hand activities; CCOS score of 15 points). Furthermore, no neurological or wound complications occurred in any patient. No CSF leaks, wound infections, or pseudomeningocele were identified during follow-up. In principle, reliable fluid-tight closure of the dura mater could be achieved with the aid of Lyoplant®. Foreign body reaction due to the inserted bovine material could not be detected either. In addition, the author evaluates the handling, the suturability and the fluid tightness positively and as decisive for the choice of Lyoplant® for performing duraplasty. The users deliberately decided against the use of autologous material, as this would have meant a further incision on the patient and associated risks.

Basically, based on the available data, it can be assumed that Lyoplant® is safe and reliable to use within the scope of its intended use. (6)

The data collected by WONG et al. on the performance of decompressive craniectomy show that both nonabsorbable (Neuro-Patch®; polyester urethane) and absorbable dura substitutes (Lyoplant®; bovine collagen) provide a reliable clinical outcome. In 21 patients, a craniectomy was performed and the above-mentioned replacement materials were used to repair the dura defect. No patients subsequently experienced wound infections, nor did they require reoperations due to wound healing disorders or other complications (e.g., CSF leakage). In one patient, the patch was removed after seven days postoperatively. It is unclear whether the patch was a Neuro-Patch® or Lyoplant® and what was the reason for the reoperation. This is also the biggest disadvantage of the study, as it is not clear how many of the 21 patients were treated with Neuro-Patch® or Lyoplant®. However, since basically no complications were described in connection with the dura replacement materials used, the application of Lyoplant® can be considered safe and reliable. (7)

In a case report, NOURKAMI-TUDTIBI et al. describe complications after major reconstruction that are probably related to the Lyoplant® used. Five years after initial diagnosis and subtotal resection of the tumor, a 12-year-old female patient was found to have an increase in residual tumor tissue on MRI follow-up, but without any noticeable symptoms. During further treatment, a removal of the tumor with subsequent dura reconstruction using Lyoplant® was performed. In the postoperative course severe neurological symptoms developed with signs of nystagmus, double vision and reduced left-sided gross motor function. One week after surgery, the patient developed severe headache, a fever of 39.5 °C and nuchal rigidity. Analysis of the CSF suggests that the symptoms, which resemble aseptic meningitis, are due to the dura substitute material used. It would have been interesting to have information on the initial partial resection of the tumor with regard to a dura reconstruction and the dura substitute material used. In this case, the

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responsible physicians decided against a revision of the patch material and successfully treated the symptoms conservatively. These foreign body reactions are extremely rare. In principle, the clinical data already available for Lyoplant® would reflect these kind of complications (see clinical studies conducted, market data and other product-related literature), so that it must be assumed that this is a rare individual case. (2)

Frontal sinus repair is a complex neurosurgical challenge. Opening the frontal sinus, either traumatically or intentionally, creates a contaminated wound that must be treated along with the associated pathology. The repair must also be designed to avoid acute and chronic complications such as CSF leakage, infection, and mucocele. Cranialization has been considered the standard procedure in frontal sinus repair in recent decades, although sinus-preserving techniques have been established more recently. In their article, MILLER et al. describe their results on preservation of the frontal sinus after traumatic injury or intentional intrusion using the compartmentalization method. The focus of this procedure is to prevent the connection between the intracranial and extracranial compartments while allowing the frontal sinus to continue to function. By ensuring separation of the two compartments with allograft and pedicled periosteum, the dural repair need only match the standard of a typical supratentorial craniotomy. The present retrospective evaluation includes 23 procedures, six of which were trauma-related and 17 tumor-related. The aim of the study was to describe the surgical technique of compartmentalization of the frontal sinus and to evaluate its performance and safety in terms of complication rate. The average follow-up was 37.5 months. Lyoplant® was used for defect coverage of the dura mater in all cases. No CSF leaks or mucoceles were observed in either tumor or trauma patients. In one patient, anemia and suspected meningitis occurred in the postoperative course, which was successfully treated conservatively with antibiotics. Furthermore, headache and incisional pain (21.7%) occurred in five patients each; maxillary sinusitis was observed in another patient (4.3%). Although the use of Lyoplant® is not the main focus of the publication, the application seems to be safe and reliable considering the documented complications.

5.4 An overall summary of the clinical performance and safety

Safety and performance indicators which require support from relevant clinical data were defined and described. All indicators depend on factors that can be controlled by the manufacturer (e.g. material and manufacturing) as well as on situation-specific factors (e.g. surgical application, patient-specific factors), as well as on the surgical use and handling.

According to the current knowledge based on the state of the art as well as the product-specific datasets provided by tests, clinical data and scientific literature, the benefits overweigh the risks of the application of Lyoplant®. The analysis and assessment of potential risks has shown that there are no increased residual risks for patients, users or third parties in the context of the intended use of Lyoplant® which can be confirmed by the product-related clinical data. Risk reduction measures also were adequate.

The indications, contraindications and intended use defined for Lyoplant® are clearly defined and cover an area that enables the user to achieve the expected goals, namely the safe and reliable covering of defects of the dura mater in cranial and spinal neurosurgical procedures.

The information materials provided by the manufacturer contain all relevant information to enable the user to a safe and reliable application of Lyoplant® within its intended use. Regarding the suitability of the intended population for the application of the device, this can be confirmed by the presented clinical data. Furthermore, suitable evidence for the performance claims is available. The information presented in the IFU as well as in the various promotion materials are consistent and correct.

In addition, PMCF-measures will be implemented (e.g., continuous literature monitoring, retrospective data analysis), so that a continuously and close monitoring for the application of Lyoplant® can be guaranteed.

In conclusion, the presented and evaluated data in this report confirms the safety and clinical performance of Lyoplant®. Therefore, from a clinical point of view, the risk-to-benefit ratio is still regarded as positive.

5.5 Ongoing or planned post-market clinical follow-up

No.	PMCF measure	Aim of measure	Status
1	Market feedback (Complaint data review)	Analyze reported production and device failures as well as difficulties in product handling.	Ongoing
2	Review of regulatory databases	Analyze reported failures concerning the device and equivalent or similar competitor devices	Ongoing
3	Retrospective study	Confirming the safety and performance of Lyoplant® as well as identifying previously unknown and evaluate currently known side-effects (related to the procedures or the medical devices).	In progress
4	User survey	Confirming the safety and performance of Lyoplant® in the pediatric population as well as identifying previously unknown side-effects	In progress
5	Clinical data from literature	Safety and performance, monitoring of potential negative information	Ongoing

6 Possible diagnostic or therapeutic alternatives

In order to ensure a safe closure of the dura mater, the user can choose from various methods and materials. Primary closure of the dura mater as preferred treatment method is still valid. If this is not possible, dura mater defects can be treated satisfactorily with the help of replacement materials. The use of autologous tissues (e. g. fascia lata, temporal fascia) is primarily used here as they cause only minor foreign body reactions. The disadvantages of these are the limited availability with regard to the treatment of larger dura defects and the additional incision for harvesting the graft, which represents an additional risk

of infection. Materials of animal origin such a porcine or bovine collagen are characterized by a low foreign body reaction. Furthermore, they are absorbed by the body over time and support cell proliferation and tissue regeneration. The use of absorbable or nonabsorbable synthetic materials for dura replacement can reduce these risks, but complications due to adhesions, infections or CSF leakage due to needle penetration during fixation of the implant may also occur. Furthermore, synthetic materials offer an inert alternative that can be manufactured indefinitely with good handling qualities like strength, elasticity, malleability, and resistance to traction.

7 Suggested profile and training for users

The user should be a neurosurgeon. No additional training is required.

8 Reference to any harmonized standards and CS applied

Standard		Issue date	Title	Product specific	Harmonized under MDR	Applied in full (F) or in part (P)
EN ISO	11135	2014/ A1:2019	Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices	N	N	F
EN ISO	13485	2016/ AC:2018/ A11:2021	Medical devices - Quality management systems - Requirements for regulatory purposes	N	Y	F
EN ISO	14155	2020	Clinical investigation of medical devices for human subjects - Good clinical practice	N	N	F
EN ISO	14630	2013	Non-active surgical implants - General requirements	Y	N	P
EN ISO	14937	2009	Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices	N	N	F
EN ISO	14971	2019/ A11:2021	Medical devices - Application of risk management to medical devices	N	N	F
EN ISO	20417	2021	Medical devices - Information to be supplied by the manufacturer (ISO 20417:2021, Corrected version 2021-12)	N	N	F
EN ISO	10993-1	2020	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2018, including corrected version 2018-10)	N	N	F
EN ISO	10993-2	2006	Biological evaluation of medical devices - Part 2: Animal welfare requirements	N	N	F

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EN ISO	10993-3	2014	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	N	N	F
EN ISO	10993-4	2017	Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood	N	N	F
EN ISO	10993-5	2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009)	N	N	F
EN ISO	10993-6	2016	Biological evaluation of medical devices - Part 6: Tests for local effects after implantation	N	N	F
EN ISO	10993-7	2008/ AC:2009	Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals	N	N	F
EN ISO	10993-9	2021	Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products	N	Y	F
EN ISO	10993-10	2013	Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization	N	N	F
EN ISO	10993-11	2018	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity	N	N	F
EN ISO	10993-12	2021	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials	N	Y	F
EN ISO	10993-16	2017	Biological evaluation of medical devices - Part 16: Toxicokinetic study design for degradation products and leachables	N	N	F
EN ISO	10993-18	2020	Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process	N	N	F
ISO/TS	10993-20	2006	Biological evaluation of medical devices - Part 20: Principles and methods for immunotoxicology testing of medical devices	N	N	F
EN ISO	10993-23	2021	Biological evaluation of medical devices - Part 23: Tests for irritation	N	Y	F
EN ISO	11607-1	2020	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems	N	N	F
EN ISO	11607-2	2020	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019)	N	N	F
EN ISO	11737-1	2018/ A1:2021	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products	N	Y	F
EN ISO	11737-2	2020	Sterilization of health care products - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process	N	Y	F
EN ISO	14644-1	2015	Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration	N	N	F

EN ISO	15223-1	2021	Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements	N	Y	P
EN ISO	22442-1	2020	Medical devices utilizing animal tissues and their derivatives - Part 1: Application of risk management	Y	N	F
EN ISO	22442-2	2020	Medical devices utilizing animal tissues and their derivatives - Part 2: Controls on sourcing, collection and handling	Y	N	F
EN ISO	22442-3	2007	Medical devices utilizing animal tissues and their derivatives - Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents	Y	N	F
EN	556-1	2001/ AC:2006	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices	N	N	F
EN	62366-1	2015/ AC:2015/ A1:2020	Medical devices - Part 1: Application of usability engineering to medical devices	N	N	F
EN	868-5	2018	Packaging for terminally sterilized medical devices - Part 5: Sealable pouches and reels of porous materials and plastic film construction - Requirements and test methods	N	N	F

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 an Implant card or the Instructions for Use to provide information on the safe use of the device.

List of abbreviation / glossary

Basic UDI-DI	Unique device identification device identifier (An identification number that is not for a specific product but for a group of products with similar intended use)
CAPA	Corrective and preventive action (consists of improvements to the manufacturers processes taken to eliminate causes of non-conformities or other undesirable situations)
CE	Conformité Européenne
CSF	Cerebrospinal fluid (clear, colorless body fluid found in the brain and spinal cord)
FSCA	Field safety corrective action (FSCA is an action taken by a manufacturer to report any technical or medical reason leading to a systematic recall of devices of the same type by the manufacturer to the National Competent Authority.
FSN	Field safety notice (Communication to customers and/or users sent out by a manufacturer or its representative in relation to a Field Safety Corrective Action)

1 Device identification and general information

1.1 Device trade name

Lyoplant®

Table 3: Lyoplant® - Article list

REF	DIM	Box content
1066021	LYOPLANT 6 cm x 14 cm	1 piece
1066030	LYOPLANT 8 cm x 9 cm	1 piece
1066048	LYOPLANT 4 cm x 10 cm	1 piece
1066050	LYOPLANT 5 cm x 6 cm	1 piece
1066064	LYOPLANT 4 cm x 5 cm	2 pieces
1066080	LYOPLANT 2 cm x 10 cm	2 pieces
1066102	LYOPLANT 1.5 cm x 3 cm	2 pieces
1066242	LYOPLANT 6 cm x 8 cm	1 piece

1.2 Manufacturer: name and address

Aesculap AG

Am Aesculap-Platz

78532 Tuttlingen/Germany

1.3 Basic UDI-DI

Basic UDI-DI for Lyoplant®: 403923900000150529

1.4 Year when the device was first CE-marked

Lyoplant® is CE marked[1] since 1997.

[1] **CE marking** is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area (EEA). The CE marking is also found on products sold outside the EEA that are manufactured in, or designed to be sold in the EEA.

2 Intended use of the device

2.1 Intended purpose

Lyoplant® is an implant of purified collagen obtained from bovine[2] pericardium. It is intended to be used as a dura mater substitute in neurosurgery. (Further information can be found in chapter *5.1 Clinical background of the device*).

2.2 Indication(s) and target population(s)

Replacement and extension of connective tissue structure in neurosurgery:

- For covering cerebral[3] and cerebellar[4] dura[5] defects
- For cerebral decompression surgery[6] when there is elevated intracranial[7] pressure
- For covering spinal dura defects
- For spinal decompression surgery[8]

There is no restriction regarding the intended patient population additional to the indications/contraindications.

2.3 Absolute contraindications

Lyoplant® should not be applied:

- In infected regions
- To replace connective tissue structures that are subject to mechanical stress
- In case of known hypersensitivity[9] against proteins of bovine origin

2.4 Relative contraindications

The following conditions, individual or combined, can lead to delayed healing or compromise the success of the operation:

- Medical or surgical conditions (e.g., comorbidities) which could hinder the success of the operation.

In the presence of relative contraindications, the user decides individually regarding the use of the product.

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[2] **Bovine:** Animal material derived from cattle.

[3] **Cerebral**: related to the brain

[4] **Cerebellar**: Relating to the part of the brain at the back of the skull, which coordinates and regulates muscular activity.

[5] **Dura:** Synonym: dura mater. The outermost brain membrane that encloses the central nervous system.

[6] **Cerebral decompression surgery** is a surgical procedure intended to relieve pressure on the skull

[7] **Intracranial:** Inside the skull.

[8] **Spinal decompression surgery** is a surgical procedure intended to relieve pressure on the spinal cord or on one or more compressed nerve roots passing through or exiting the spinal column.

[9] **Hypersensitivity**: Excessive response to the stimulus of a foreign agent, such as an allergen.

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3 Device description

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

Lyoplant® is a pure collagen implant obtained from bovine pericardium. The membrane is used for the replacement and extension of connective tissue structures in neurosurgery. During the intended use the following organs, tissue, body fluids come in contact with the device: brain, spinal cord, bone, dura mater, cerebrospinal fluid as well as blood. The lyophilization (freeze-drying) process guarantees that Lyoplant® retains its loose fibrous structure to offer appropriate conditions for integration after implantation (Figure 2).

Figure 2: Product image of Lyoplant® (left); loose fibrous structure of Lyoplant® (right).

Lyoplant® belongs to the neurosurgical implants.

- During the intended use the following organs/tissue/body fluids come in contact with the device: brain, spinal cord, bone, dura mater, cerebrospinal fluid as well as blood.
- The devices are necessarily used together with non-absorbable sutures.
- The application of the devices is invasive.
- The application period of the devices is long-term.
- The devices are intended for clinical users: Surgeons with required knowledge about the surgical technique and surgical training who are aware about the in vivo characteristics of the product, operating room personnel (set-up, handling, functional check).
- Lyoplant® implants are for single use and are shipped in a sterile way. They will be sterilized by ethylene oxide.
- The devices do not contain pharmaceutical components or human tissue; they are neither blood products nor radioactive.

3.2 Information about medicinal substances in the device, if any

Lyoplant® doesn't contain any medicinal substances.

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

Before implantation, Lyoplant® is cut as closely as possible to the defect size and rehydrated in sterile solution to achieve tension-free embedding. It must be sutured and should be fixed with non-absorbable suture material using atraumatic round-bodied needles. An additional fixation with fibrin glue is possible. Lyoplant® resorbs within one to three months after implantation.

3.4 Description of accessories, if any

Not applicable.

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

Potential risks have been identified and controlled according to *DIN EN ISO 14971 Medical devices - Application of risk management to medical devices*.

4.2 Remaining risks and undesirable effects

The general risks associated with surgery are assumed known and are therefore not described.

Within the scope of the legal obligation to provide information, reference is made to the typical risks, interactions and side effects listed below.

Possible risks, side effects and interactions of the application currently known to the manufacturer are:

- CSF-Leakage[10]
- Infection[11]
- Adhesions[12]
- Allergic reactions to proteins of bovine origin

Compared to the application of alternative dura substitutes, the occurrence rates of the abovementioned risks during the use of Lyoplant® can be regarded as acceptable.

Note:

The points mentioned above include potential clinical consequences.

No risks, side effects and interactions as a result of comorbidities of the patient have been identified.

4.3 Warnings and precautions

Safety with regard to the transmission of zoo-anthroponoses

In view of the fact that bovine material from New Zealand is regarded as safe by the European authorities with respect to BSE (bovine spongiform encephalopathy), the raw material is imported from there. Furthermore, Lyoplant® is subjected to treatment with NaOH during processing, in order to further reduce any theoretical risk, by means of this recognized decontamination method.

[10] **CSF-Leakage** is an involuntary discharge of cerebrospinal fluid (CSF).

[11] **Infection**: A disease caused by germs or bacteria.

[12] **Adhesion** is a union of two surfaces that are normally separate.

MRI Safety Information

MRI examinations using magnetic fields of 1.5 or 3.0 tesla do not present an additional risk to implant bearers as the product is made of non-metallic material.

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

When necessary, field safety corrective actions or field safety notifications were issued regarding the products. For Lyoplant® neither Field Safety Notices (FNS), Field Safety Corrective Actions (FSCA) nor Corrective and Preventive Actions (CAPA) were required.

5 Summary of clinical evaluation and post-market clinical follow-up

5.1 Clinical background of the device

Lyoplant® is used in neurosurgery as dura mater replacement. The dura mater is the outermost of the three types of brain skin, also called meninges. Together with the arachnoidea and the pia mater it builds the enclosing of the brain and the spinal cord. The meninges encapsulate the central nervous system and prevent a loss of cerebrospinal fluid (CSF). CSF protects the nervous system from mechanical influences and plays a role in maintaining cerebral metabolic balance and is also necessary for temperature control. After cranial or spinal neurosurgery in which an opening of the brain skin was required, the dura mater opening is preferably closed by suturing. In some cases, like the removal of tumors (such as meningioma or glioma), craniectomy e. g. therapy of Chiari malformation, the dura mater may be surgically removed, may shrink or be harmed during the procedure. The dura loss requires a sufficient dura replacement by a graft to avoid CSF leakage associated complications, which can manifest as peridural[13] collection of CSF, meningitis[14], cerebritis[15] or brain abscess[16].

5.2 The clinical evidence for the CE-marking

Clinical evidence for CE-marking is based on laboratory testing, scientific literature, market feedback and clinical data with the devices from clinical studies.

5.3 Safety

According to the analysis of the market feedback, the data generated in a clinical study with implants and the scientific literature, no systematic failures or complications related to Lyoplant® were observed. Thus, the safety of the Lyoplant® is confirmed.

[13] **Peridural:** Anatomical location occurring in the area of the spinal cord membranes or spinal canal

[14] **Meningitis:** Inflammation of the pia mater and arachnoid mater.

[15] **Cerebritis:** Inflammation of the brain.

[16] **Brain abscess:** An encapsulated inflammation of the brain caused by bacteria or foreign bodies.

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6 Possible diagnostic or therapeutic alternatives

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

6.1 General description of therapeutic alternatives

In order to ensure a safe closure of the dura mater, the user can choose from various methods and materials. Closure of the defect by suturing (also called primary closure) as preferred treatment method is still valid. If this is not possible, dura mater defects can be treated satisfactorily with the help of replacement materials. The use of autologous tissues[17] (e. g. fascia lata, temporal fascia) is primarily used here as they cause only minor foreign body reactions. The disadvantages of these are the limited availability regarding the treatment of larger dura defects and the additional incision for harvesting the graft, which represents an additional risk of infection. Materials of animal origin (xenografts[18]) are characterized by a low risk of foreign body reaction. Furthermore, they are absorbed by the body over time and support cell proliferation[19] and tissue regeneration. However, there is a risk of transmission of zoonoses[20] when using these materials which can reduced by suitable cleaning and manufacturing processes.

The use of absorbable or nonabsorbable synthetic materials for dura replacement can reduce these risks, but complications due to adhesions, infections or CSF leakage due to needle penetration during fixation of the implant may also occur. Furthermore, synthetic materials offer an alternative that can be manufactured unlimited with good handling qualities like strength, elasticity, malleability, and resistance to traction. Scientific literature reviews showing that different dura replacement materials are preferred in different indications due to their material properties so that the application of the different dura substitutes depend on the localization as well as the preferences of the surgeon regarding the material properties and handling characteristics of the different materials. Therefore, the use of dura grafts like Lyoplant®, made of xenogeneic origin, can still be regarded as safe and reliable for the treatment of dura defects.

7 Suggested training for users

The user should be a neurosurgeon. No additional training is required.

8 Signatures and revision history

This document is signed electronically (see last page).

[17] **Autograft or autologous material**: A tissue or organ that is transplanted from one part to another of the same body

[18] **Xenograft**: A graft of tissue taken from a donor of one species (e. g. cattle, horse) and grafted into a recipient of another species

[19] **Cell proliferation:** The rapid growth of cells or microorganisms.

[20] **Zoonosis:** Diseases transmissible from animals to humans and vice versa from humans to animals.

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No.	Type of Revision	Date	Revision validated by the Notified Body
1.0	Initial preparation of the SSCP	16.09.2021	N/A
2.0	Expansion of the SSCP to include the patient-specific part, due to the implementation of an implant card.	23.09.2021	N/A
3.0	Textual changes to assure consistency in CEP, CER, and IFU.	14.06.2022	N/A
4.0	Changes due to feedback from the notified body in the context of a certification according to the MDR 2017/745: - Textual changes in Part 1, Section 3.1 Description of the device - Update of Section 5.5. Ongoing or planned post-market clinical follow-up - Textual changes in Part 1, Chapter 8 Reference to any harmonized standards and CS applied	29.07.2022	N/A
5.0	Changes due to feedback from the notified body in the context of a certification according to the MDR 2017/745: - Textual changes in Part 1, Chapter 8 Reference to any harmonized standards and CS applied	19.09.2022	N/A
6.0	Changes due to feedback from the notified body in the context of a certification according to the MDR 2017/745: - update of the revision number on the title page, - textual changes in 1.6 Class of device, i.e., rule 8.2 was removed according to Annex VIII, chapter II, 3.5.	See "Effective Date" on approved document	Not yet validated by the Notified Body. Validation language: English

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