Summary of Safety and Clinical Performance

Lyoplant® Onlay

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
BSE	Bovine Spongiform Encephalopathy
CAPA	Corrective and preventive action
CCOS	Chicago Chiari Outcome Scale
CE	Conformité Européenne
CSF	Cerebrospinal fluid
DIN	Deutsches Institut für Normung (English: German Institute for Standardization)
EEA	Endonasal Endoscopic Approach
EN	European Norm
FSCA	Field safety corrective action
FSN	Field safety notice
IHFL	intra-operative high flow CSF leaks
ILFL	intra-operative low flow CSF leaks
INL	intra-operative no CSF leaks
ISO	International Organization for Standardization
MDR	Medical Device Regulation
MRI	Magnetic Resonance Imaging
NB	Notified Body
PMCF	Post-market Clinical Follow-up
POL	Postoperative CSF Leak
SB	Spina Bifida
SEM	Scanning Electron Microscope
SRN	Manufacturer's single registration number
SSCP	Summary of Safety and Clinical Performance
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® Onlay

Table 1: Delivery forms and packaging sizes

Article number	Size	Content
1067010	2.5 cm x 2.5 cm	1 piece
1067020	5.0 cm x 5.0 cm	1 piece
1067030	2.5 cm x 7.5 cm	1 piece
1067040	7.5 cm x 7.5 cm	1 piece
1067050	10.0 cm x 12.5 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® Onlay: 40392390000015062B

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® Onlay is CE-certified since 2013-05-03.

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® Onlay is an implant of purified collagen obtained from bovine pericardium and bovine split hide. 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 are no restrictions regarding the intended patient population additional to the indications and contraindications (see 2.3).

2.3 Contraindications and/or limitations

2.3.1 Absolute contradictions:

Lyoplant® Onlay 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

2.3.2 Relative contradictions

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® Onlay is a resorbable implant used for the replacement and extension of dura mater in neurosurgery to prevent cerebrospinal fluid leakage.

Before implantation, a suitable implant size for the sealing of the defect is selected. Lyoplant® Onlay can either be applied onlay or sutured. If Lyoplant® Onlay is applied onlay, the edges of the implant should overlap the surrounding dura by approximately 1 cm. The fleece-like porous side (labeled “Dura side”, see Figure 1) must face the dura. If the implant is sutured, it should be cut as closely as possible to the defect size. To achieve tension-free embedding, the implant is rehydrated in sterile solution before implantation. Lyoplant® Onlay resorbs within one to three months after implantation.

Lyoplant® Onlay is a two-layered implant made of purified collagen (type I/III) obtained from bovine pericardium and bovine split hide (composition: 12 ± 4 mg/cm² pericardium; 10 ± 2 mg/cm² spongy components). The thickness of the bilayer product is specified to 1.5 mm - 5.0 mm, the weight per unit area is specified to 160 – 280 g/m². The overall porosity of Lyoplant® Onlay is 70 ± 5%.

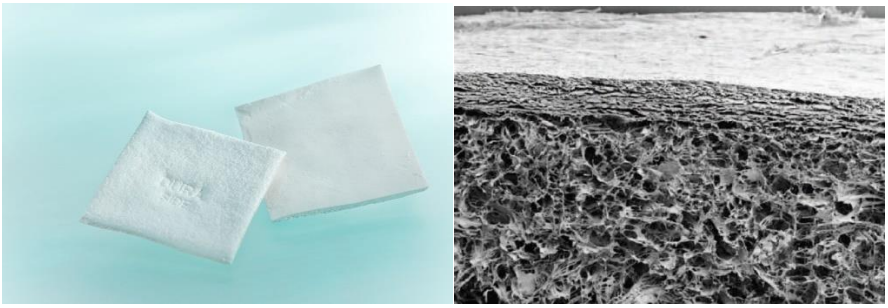

Figure 1: Lyoplant® Onlay product picture (left) and SEM image (right)

Lyoplant® Onlay is cleansed of non-collagenous components such as enzymes, lipids and non-collagenous proteins by the special preparation process. Lyoplant® Onlay is not chemically cross-linked.

Lyoplant® Onlay 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.
- If Lyoplant® Onlay is sutured, the implant should be fixed with non-absorbable suture material using atraumatic round-bodied needles. An additional fixation with fibrin glue is possible.
- 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® Onlay 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 2013, the following changes have been issued:

2014-10-23: Change of packaging material

2015-01-26: Additional suppliers for animal origin material

2017-01-19: Change of packaging material

2017-06-30: Change of sterilization site

2017-05-02: Change of labels and tolerance limits for thickness

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

No additional accessories are required for the application of Lyoplant® Onlay. Additional fixation by suturing or fibrin glue is possible. If Lyoplant® Onlay is sutured, the implant should be fixed with non-absorbable suture material using atraumatic round-bodied needles.

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® Onlay as well as the results of clinical studies held by the manufacturer, CSF leaks are a common complication with incidence rates from 1.87 % to 7.0%. Furthermore, incidence rates from 0.0% to 2.8% for infections depending on the postoperative endpoint (0.93% two days postoperatively, 2.8% before discharge and 0.0% at the 3-month follow-up) have been reported.

In the abovementioned clinical data, foreign body reactions such as allergic reactions due to material incompatibilities or adhesions to the surrounding tissue were not reported for Lyoplant® Onlay. 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

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.

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® Onlay is subjected to treatment with NaOH during processing, in order to further reduce any theoretical risk, by means of this recognized decontamination method.

Notes and details of stability

- Store implant components in their original packaging. Remove them from their original protective packaging only just prior to implantation.
- Do not use products from open or damaged sterile packaging.
- Do not use the product after its use-by date.
- Dispose of any implant pieces not required intraoperatively. If the product is reused, the patient may suffer infection and the implant may lose its function. There are risks in the form of injury, illness or death from contamination and/or restricted functionality of the product.
- Do not reuse the product. The product must not be resterilized because the structure of the implant and thus its in vivo behavior may be adversely changed.
- Do not reprocess the product.

  Store sterile packed implant components dust-protected in a dry, dark room.

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 were necessary for the products of Lyoplant® Onlay since its introduction in the market. One corrective and preventive action (CAPA) was planned and conducted in 2015.

Deviations occurred in the production process of homogenizing the collagen suspension, which resulted in a pH deviation (pH too high). The cause of this deviation was a too short rinsing time, which was set by an external employee during machine maintenance to perform the maintenance faster. Subsequently, the default setting was not restored, and no check of the parameters was performed by B.Braun Aesculap. As a corrective measure, the creation of a process for checking maintenance activities, including appropriate documentation, was carried out. In addition, all machines were checked for unauthorized changes regarding the relevant machine parameters at all facilities. This deviation had no influence on the product (viscosity and processability of the material corresponded to the specifications). There was no risk to patients, users or third parties. The CAPA was closed in 2017.

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

Not applicable.

5.3 Summary of clinical data from other sources, if applicable

Clinical studies

LYON study report

Date: 2019-11-21

The report of this prospective, observational (non-interventional), single-arm cohort study includes data from 61 patients recruited from three study sites. Lyoplant® Onlay was used by a variety of surgeons with different levels of experience. Both cranial and spinal cases with a wide range of different dura defect sizes were included. The primary end point was the incidence of reoperation due to CSF leakage up to the day of discharge. There were no reoperations due to CSF leaks both up to discharge and follow-up (approximately 4 months postoperatively). CSF leaks were observed in four patients. The incidence rate of 7 % is within the range reported in the literature. These adverse events were found to be causally related to Lyoplant® Onlay but were reported as non-serious complications without the need for surgical intervention and resolved without sequelae. The handling characteristics of Lyoplant® Onlay (such as ease of

cutting, tensile strength, adaptation to the tissue, onlay effect, suture retention strength) were rated positively in all categories assessed. The wound was judged to be tight and dry at discharge and follow-up in all cases. Subcutaneous swelling and subcutaneous fluid collections occurred infrequently.

Additional fluid collections, edema, and swelling were observed on external radiological analysis of routine postoperative MRI/CT scans at discharge and follow-up. However, they were clinically unremarkable and considered normal postoperative findings. These results demonstrate that Lyoplant® Onlay is a safe and efficient dura replacement.

Comparative study Lyoplant® Onlay and DuraForm in China

As part of a pivotal study for the market launch of Lyoplant® Onlay in China, the safety and performance of Lyoplant® Onlay was compared with the comparator product Duraform (Codman & Shurtleff, Inc., see chapter 4.3 of the CER) using a prospective, multicenter, randomized and controlled study design. For this purpose, 256 patients (Lyoplant® Onlay: n=129; Duraform: n=127) were included in the study. The primary endpoint of the study was defined as the occurrence of CSF leakage 90 days postoperatively. No statistically significant difference was found between Lyoplant® Onlay and Duraform. For the occurrence of infections, no significant difference between the test and control group could be observed over the entire follow-up period (90 ± 10 days).

In the test group, 691 adverse events occurred in 123 subjects; in the control group, 615 adverse events occurred in the 119 subjects. In the test group, 10 adverse events related to Lyoplant® Onlay occurred in three subjects, whereas in the control group, 30 adverse events related to Duraform occurred in 8 subjects (incidence rate: 2.44% vs. 6.72%). The difference between the two groups was not statistically significant. In the test group, 12 serious adverse events occurred in 10 subjects; in the control group, 16 serious adverse events were documented in 15 subjects (8.13% vs. 12.61%). The difference between the two groups was not statistically significant. No serious adverse events related to Lyoplant® Onlay occurred in the test group; in the control group, one serious adverse event related to the investigational product occurred in one patient (0% vs. 0.84%). The difference between the two groups was not statistically significant. Furthermore, three subjects in the test group experienced three adverse events that led to study discontinuation. In contrast, four patients in the control group were unable to continue the study due to seven adverse events. The difference between the two groups was not statistically significant.

Regarding the handling of Lyoplant Onlay, user satisfaction was generally very high. In most cases, handling was rated as excellent (76.64%), good (20.56%) or moderate (2.8%). In particular, the parameters of material thickness, sealing quality, fitting effect and tear resistance of the material were convincing and were rated excellent in more than 75% of cases. As far as assessable, the suture strength (50.47%), needle penetration (52.34%), and suturability (64.49%) were also predominantly rated as excellent. In only a few cases was suturability rated as unacceptable in terms of suture strength and needle penetration (0.93% each). It can therefore be concluded that Lyoplant® Onlay can be used safely and reliably within its intended use and provides comparable clinical results to Dura-form.

Customer survey – results

Effective

The aim of the user survey was to determine users' initial experiences with Lyoplant® Onlay and to identify potential risks and problems associated with the application of the dura substitute. The survey includes the assessment of 21 users from 12 different clinics in Germany (period: 06/2013 to 09/2013) and 12 user surveys from 8 different clinics in the USA (period: 12/2013 to 08/2015). In Germany, 15 applications were performed onlay and 6 with the underlay technique. In eight of these procedures, sutures were used as supplementary fixation. The applications performed in the USA were applied using the onlay technique in four cases. In seven cases, the surgeons opted for supportive fixation using sutures. The physicians surveyed used Lyoplant® Onlay in various cranial and spinal indications (e.g., closure of dural defects, after tumor resection, craniotomy, laminectomy).

In addition to recording the duration of surgery, the defect size of the dura mater and the rehydration time, aspects of functionality and handling were evaluated in particular (e. g. ability to cut, elasticity, tensile strength, thickness, liquor-tight sealing, ease of use). The evaluation of the individual aspects was performed using a 10-point scale, where 1 (=very poor) and 10 (=very good).

In general, the material properties of Lyoplant® were rated in the range of Ø5.88 to Ø8.18 by the respondents in Germany and Ø8.67 to Ø9.45 by the respondents in the USA. According to the survey, the identification of the “Dura-Side” for the intended application was easily possible.

Finally, it can be concluded that it is evident from the user survey that the surgeons surveyed rate the use of Lyoplant® Onlay as very positive.

Expert Reports

Expert Report University Clinic Leipzig – Prof. Dr. med Nestler

In this expert report the author described his experiences using Lyoplant® Onlay in 31 cases between 2013 and 2015. In many cases Lyoplant® Onlay were used after the removal of posterior fossa tumors partly with opening of the fourth ventricle. In most convexity craniotomies, meningioma removal required dura reconstruction, a few intraventricular lesions were resected. Up to the preparation of this expert report neither CSF leakage nor surgical site infection have been observed after the application of Lyoplant® Onlay. In one case of transventricular resection of a pituitary adenoma in the third ventricle, subdural hygroma has occurred beneath the craniotomy. Nestler concluded that Lyoplant® Onlay is suitable especially in locations in which suturing of the implants into place is not possible, due to poor quality of anchoring tissue. Nevertheless, he stated that a kind of fixation is needed to secure the implant from sliding out of place. Furthermore, the author described the handling properties as fast, safe and easy, shows less stiffness and provides faster watertight closure compared to other products. Also, less fixation is needed and good adaption to the defect is possible.

Expert Report Klinikum Darmstadt GmbH – Dr. med. Frank Bode

This report documents the first experience of using Lyoplant® Onlay at the Hospital Darmstadt between 2013 – 2016 in 43 cases. Analogue to the experiences of PD Nestler, no CSF leakage or infections have been observed. Bode concludes an easy adjustment to the dura defect by cutting and easy, fast and safe application of Lyoplant® Onlay. Especially in larger dura defects Lyoplant® Onlay is suitable for the treatment of dura defects and has good self-fixation ability by adherence to the dura.

Literature on the product

In a retrospective, single-center analysis by DI PERNA et al. Investigated the effectiveness of different adopted reconstruction strategies in patients that underwent Endoscopic Endonasal Approach (EEA). This analysis includes data of patients (n=566) who were affected by skull base neoplasms and therefore underwent EEA between January 2012 and December 2019. CSF leaks occurring during surgical procedures were divided into 3 groups: intra-operative no CSF leaks (INL), intra-operative low flow CSF leaks (ILFL) and intra-operative high flow CSF leaks (IHFL). For the reconstruction of the skull base different treatment options are available depending on the defect size, anatomical site of surgical location, grade of intraoperative leakage and type of tumor. Regarding these parameters the use of dural substitutes (e.g., Lyoplant® Onlay, Redura, or DuraGen) were used in inlay or onlay fashion. Unfortunately, no separate analysis of the different dura substitutes was performed. Next to the use of dura substitutes, different autologous tissue was considered for the reconstruction procedure such as abdominal fat, ileo tibial tract, sinus mucosa flap, or free graft of nasal mucosa or naso-septal flap. The surgical procedure was divided into three categories: minimal reconstruction which was used for small intracranial opening without CSF leakage. In these cases, a sponge was used to fill the surgical cavity fixed with fibrin glue or a mucosal flap from sphenoid sinus have been used alternatively. In cases of standard reconstruction procedure was used, dural substitutes were used for small intracranial openings and for IFLF. Here, autologous abdominal fat and inferior or middle turbinate mucosa was often used respectively to fill the cavity and to cover the defect. Fibrin glue was then used to adhere the dural substitute and fat together. Finally, in larger defects with IHFL a “Sandwich” multilayered reconstruction was performed. The first layer consist-ed in an inlay-positioned synthetic dural substitute or an ileo tibial tract which was positioned as inlay followed by the placement of autologous abdominal fat to refill empty spaces. A second layer using dura substitutes or ileo tibial tract was then placed in onlay fashion. Another layer of abdominal fat graft is positioned extraosseous), followed by a naso-septal flap, harvested at the beginning of the surgery, is care-fully rotated on the skull base defect. (1)

Most cases received the minimal reconstruction using a sponge, fibrin glue, and mucosal flap (n=289; 55.5%). In 124 patients, standard approach using dural substitute and fat was performed (23.8%, whereas 108 patients underwent sandwich multilayer closure (20.7%). As a main result of this retrospective analysis the authors concluded that vascularized multilayered reconstruction and fat use showed to be effective in lowering post-operative CSF leaks in patients with intraoperative high flow leakage. No statistically significant differences between post-operative CSF rate and type of reconstruction were found after stratification in patients with INL or ILFL. The critical analysis of this series shows that IOL grade strongly affects POL rate. The type and the anatomical site of surgical approach should be considered during surgical planning in order to predict and assess IOL grade. No evidence of lumbar drain positioning effective-ness was found, even if it seems to be useful when IHFL was encountered. Once this aspect has been defined, tailored skull base reconstruction strategy should be chosen. A disadvantage of this long-term analysis is the fact that no subgroup analysis of the different dura substitutes was performed, so that the no evaluation of the performance of the used dura graft regarding the occurrence of postoperative CSF leakage is possible. (1)

In a prospective study by CRUZ-MARTINEZ et al. a cohort of singleton fetuses with confirmed lumbosacral open spina bifida (SB) were selected for fetal surgery. The purpose of this study was to describe the feasibility of open fetal microneurosurgery and to compare perinatal outcomes with cases managed using open fetal surgery technique. Between the study period (December 2016 and May 2020), a total of 61 cases were selected for intrauterine spina bifida repair. In the first cases (n=13) SB repair was successfully performed using the open approach. One case was excluded from the study due to an anaphylactic shock associated with the maternal cardiac arrest and fetal bradycardia, so that 47 consecutive cases, fetal myeloplasty with a complete 3-layer correction was successfully performed by open fetal microneurosurgery. In cases with myeloschisis, a 2.5 × 2.5-cm biological patch of Lyoplant® Onlay was used (n=8). (2)

No significant differences were observed in the upper level of the spinal defect, gestational age at fetal intervention, surgical times, and rate of myeloschisis between both groups. After fetal intervention, the group with open microneurosurgery showed a significantly lower rate of oligohydramnios, and PPROM, higher gestational age at birth, higher interval between fetal intervention and delivery, lower rate of preterm de livery below 34 weeks, and lower rate of perinatal death than the group with classic open surgery. No differences were observed in the rate of maternal complications such as placental abruption, pulmonary edema, chorioamnionitis, or maternal bleeding requiring blood transfusion. The rates of sub-cutaneous cerebrospinal fluid leakage requiring a complementary postnatal surgical repair and of hydrocephalus requiring either ventriculoperitoneal shunting or only endoscopic third ventriculostomy was similar between both groups. Therefore, the authors concluded that intrauterine spina repair by open fetal microneurosurgery is feasible and was associated with better perinatal outcomes than classic open fetal surgery. Lyoplant® Onlay was not in the focus of the publication, but it can be assumed that use was safe and reliable, due to the fact no complications regarding its applications were reported. (2)

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® Onlay. 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® Onlay which can be confirmed by the product-related clinical data or conducted clinical studies. Risk reduction measures also were adequate.

The indications, contraindications and intended use defined for Lyoplant® Onlay 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® Onlay 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), so that a continuously and close monitoring for the application of Lyoplant® Onlay can be guaranteed.

In conclusion, the presented and evaluated data in this report confirms the safety and clinical performance of Lyoplant® Onlay. 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 leak-age 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
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® Onlay

Table 2: Lyoplant® - Article list

Article number	Size	Content
1067010	2.5 cm x 2.5 cm	1 piece
1067020	5.0 cm x 5.0 cm	1 piece
1067030	2.5 cm x 7.5 cm	1 piece
1067040	7.5 cm x 7.5 cm	1 piece
1067050	10.0 cm x 12.5 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® Onlay: 40392390000015062B

1.4 Year when the device was first CE-marked

Lyoplant® Onlay is CE marked[1] since 2013-05-03.

[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® Onlay is an implant of purified collagen obtained from bovine[2] pericardium and bovine split hide. It is intended to be used as a dura mater[3] substitute in neurosurgery.

2.2 Indication(s) and target population(s)

Replacement and extension of connective tissue structure in neurosurgery:

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

There are no restrictions regarding the intended patient population additional to the indications and contraindications (see 2.3).

2.3 Contraindications and/or limitations

2.3.1 Absolute contradictions:

Lyoplant® Onlay 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

2.3.2 Relative contradictions

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

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

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

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

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

[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.

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

Lyoplant® Onlay is a two-layered resorbable implant used for the replacement and extension of dura mater in neurosurgery to prevent cerebrospinal fluid leakage (Figure 2). 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.

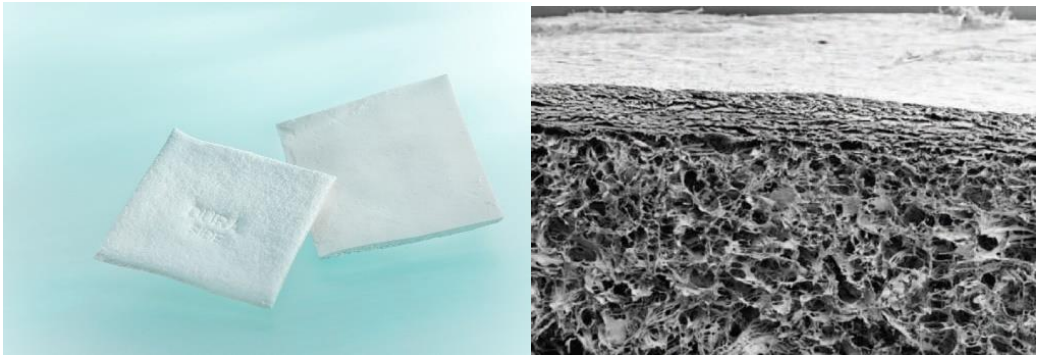

Figure 2: Lyoplant® Onlay product picture (left) and SEM image (right)

Lyoplant® Onlay resorbs within one to three months after implantation.

Lyoplant® Onlay belongs to the neurosurgical implants.

- If Lyoplant® Onlay is sutured, the implant should be fixed with non-absorbable suture material using atraumatic round-bodied needles. An additional fixation with fibrin glue is possible.
- 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 prod-uct, operating room personnel (set-up, handling, functional check).
- Lyoplant® Onlay 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® Onlay doesn't contain any medicinal substances.

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

Before implantation, a suitable implant size for the sealing of the defect is selected. Lyoplant® Onlay can either be applied onlay (without additional fixation) or sutured. If Lyoplant® Onlay is applied onlay, the edges of the implant should overlap the surrounding dura by approximately 1 cm. The fleece-like porous side (labeled “Dura side”, see) must face the dura. If the implant is sutured, it should be cut as closely as possible to the defect size. To achieve tension-free embedding, the implant is rehydrated in sterile solution before 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[9]
- Infection[10]
- Adhesions[11]
- 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® Onlay can be regarded as acceptable.

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

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

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

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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.

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® Onlay neither Field Safety Notices (FNS) nor Field Safety Corrective Actions (FSCA) were required. Since its introduction in the market, one corrective and preventive action (CAPA) was planned and conducted in 2015. A deviation in the manufacturing process caused by an incorrect set up of a machine after a maintenance procedure was identified during automatic check of pH-values.
As a corrective measure, the creation of a process for checking maintenance activities, including appropriate documentation, was carried out. This deviation had no influence on the product (viscosity and processability of the material corresponded to the specifications). There was no risk to patients, users or third parties.

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

5.1 Clinical background of the device

Lyoplant® Onlay 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

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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[12] collection of CSF, meningitis[13], cerebritis[14] or brain abscess[15].

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® Onlay were observed. Thus, the safety of the Lyoplant® Onlay is confirmed.

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[16] (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[17]) are characterized by a low risk of foreign body reaction. Furthermore, they are absorbed by the body over time and support cell proliferation[18] and tissue regeneration. However, there is a risk of transmission of zoonoses[19] when using these materials which can reduced by suitable cleaning and manufacturing processes.

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

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

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

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

[16] **Autograft or autologous tissue**: Tissue that is transplanted from one part to another of the same body.

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

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

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

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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® Onlay, 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).

No.	Type of Revision	Date	Revision validated by the Notified Body
1.0	Initial preparation of the SSCP	23.09.2021	N/A
2.0	Textual changes to assure consistency in CEP, CER, and IFU.	13.06.2022	N/A
3.0	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 Device description and material/substances in contact with patient tissues - 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
4.0	Changes due to feedback from the notified body in the context of a certification according to the MDR 2017/745:	22.09.19	N/A

	Textual changes in Part 1, Chapter 8 Reference to any harmonized standards and CS applied.		
5.0	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, - textual changes in signature and history table, i.e., the statement on validation by Notified Body in previous versions was replaced with "N/A".	See "Effective Date" on approved document	Not yet validated by the Notified Body. Validation language: English

9 Literature Cited

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2. Cruz-Martínez R, Chavelas-Ochoa F, Martínez-Rodríguez M, Aguilar-Vidales K, Gámez-Varela A, Luna-García J et al. Open Fetal Microneurosurgery for Intrauterine Spina Bifida Repair. Fetal Diagn Ther 2021; 48(3):163–73.

Title: SSCP_Lyoplant_Onlay Initiator: Izabela ? FirkowskaBoden

This document is signed electronically in compliance with the B. Braun electronic signature policies and procedures by following persons:

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Meaning: Document signed as Author
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UserName: Lange, Katharina (langktde)
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Date: Tuesday, 14 March 2023, 14:58 W. Europe Daylight Time
Meaning: Approve Document
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