De Novo Classification Request For
Coaptium Connect with Tissium Light

Regulatory Information

FDA identifies this generic type of device as:

In situ polymerizing peripheral nerve repair device. An in situ polymerizing peripheral nerve repair device is intended to be used in a peripheral nerve repair procedure and is composed of, in whole or in part, starting materials that polymerize when delivered to a peripheral nerve injury.

New Regulation Number: 21 CFR 882.5270

Classification: Class II

Product Code: SFD

Background

Device Name: COAPTIUM CONNECT with TISSIUM LIGHT

Submission Number: DEN240066

Date De Novo Received: November 21, 2024

Sponsor Information:

TISSIUM SA
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Indications for Use

The COAPTIUM CONNECT with TISSIUM LIGHT is indicated as follows:

COAPTIUM CONNECT with TISSIUM LIGHT is indicated for the sutureless repair of peripheral nerve injuries not in continuity in which a gap closure ≤ 1 cm is present or can be achieved with flexion of the extremity.

Limitations

For prescription use only.

COAPTIUM CONNECT with TISSIUM LIGHT is contraindicated in individuals with known or suspected hypersensitivity to aminated poly(glycerol sebacate) acrylate or the color additive FD&C Blue No. 1 dye (Brilliant Blue FCF).

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

COAPTIUM CONNECT is a bioabsorbable coaptation system for sutureless repair of peripheral nerve injuries not in continuity. The system includes a single-use syringe pre-filled with a photoactive COAPTIUM polymer which is used to secure an implantable three-dimensional coaptation chamber to the nerve segments that are distal and proximal to a nerve injury. The system includes two implantable components, the coaptation chamber and the COAPTIUM polymer, and three sterile disposable accessories of a silicone applicator (base and cap), a syringe tip, and a TISSIUM LIGHT cover.

The coaptation chamber and the COAPTIUM polymer are designed to serve as a protective interface between the nerve and the surrounding tissues and create a conduit for axonal growth. They are soft, flexible, and degrade through hydrolysis with a degradation profile that is compatible with nerve healing.

The silicone applicator and syringe tip are designed to deliver consistent and precise application of the COAPTIUM polymer onto the coaptation chamber and adjacent nerve. The TISSIUM LIGHT cover is used with the reusable non-sterile associated device, the TISSIUM LIGHT, which photoactivates the COAPTIUM polymer.

The components of COAPTIUM CONNECT are supplied sterile and for single use in double peel packages in a variety of sizes. The TISSIUM LIGHT cover is supplied in a single peel pack and used as a sterile barrier for the reusable TISSIUM LIGHT.

The TISSIUM LIGHT is non-sterile and supplied separately from the COAPTIUM CONNECT. The COAPTIUM CONNECT accommodates nerve diameters up to 6 mm and is available in chamber sizes up to 15 mm in length.

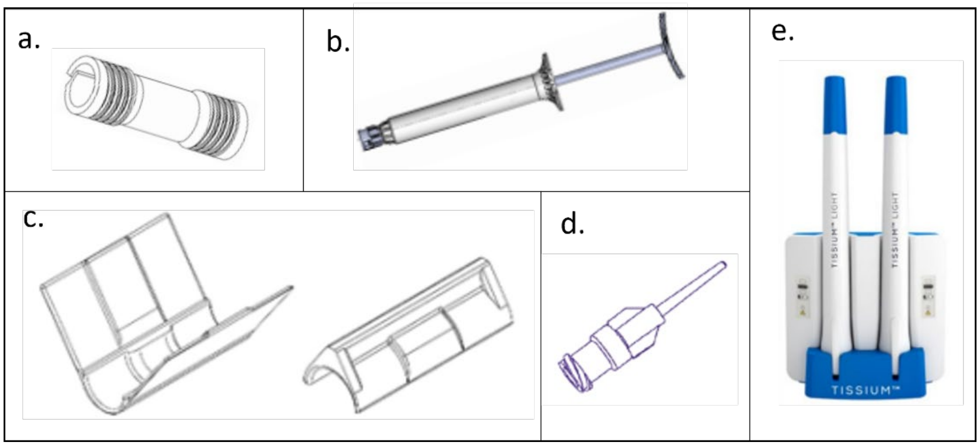

Figure 1. COAPTIUM CONNECT components: a. coaptation chamber, b. COAPTIUM polymer, c. silicone applicator, d. syringe tip, e. TISSIUM LIGHT.

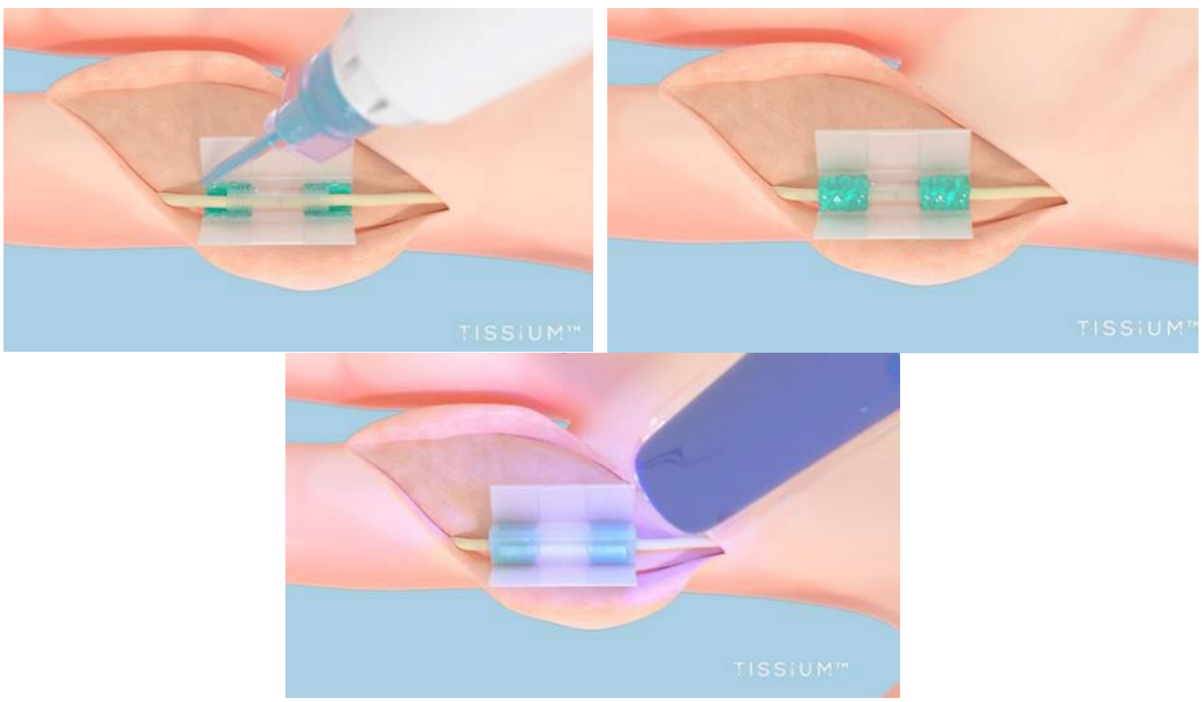

Figure 2. COAPTIUM CONNECT and TISSIUM LIGHT surgical procedure overview.

SUMMARY OF NONCLINICAL STUDIES

DEGRADATION STUDIES

A safe degradation profile of the implantable components of the COAPTIUM CONNECT has been established through *in vitro* and *in vivo* studies. Chemical studies evaluated the identities and systemic risks of degradants while animal studies evaluated the effect of those degradants on local tissue response.

ANIMAL STUDIES

The performance and safety of COAPTIUM CONNECT was assessed in an implantation study using a rat peripheral (i.e., sciatic) nerve transection model with 7-day, 30-day and 90-day time points. The test article was compared to a comparator control device and a sham surgery control (i.e., nerve exposure with no transection). The study assessed the local effects through clinical observations, a functional battery of tests to evaluate for neurologic deficiencies and functional recovery, clinical pathology, gross pathology, gastrocnemius muscle weight measurement, and histopathology of the repaired nerve and surrounding tissues, draining lymph nodes and major organs. In this study, the final polymerized device was demonstrated to maintain adherence to the nerve, without migration of the device or nerve detachment throughout the study duration. Gastrocnemius muscle weights decreased after the transection and implant procedure with the lowest weight noted at the 30-day time point; however, by 90 days significant recovery of muscle mass was noted at necropsy, suggesting partial muscle reinnervation. Histologic recovery of the nerve fibers was demonstrated by a decrease in nerve degeneration and an increase in nerve regeneration over the 3 time points by increases in axon proliferation and myelin recovery in the COAPTIUM CONNECT groups. Functional recovery as noted on functional testing was similar between the comparator control and the test article groups over the course of the study with demonstration of partial recovery of motor and sensory function through improving toe out angle scores and Von Frey scores by the final time point of 90 days. Over the course of the study, tissue reactivity scores decreased in the COAPTIUM CONNECT groups demonstrating that a steady-state was reached by the 90 day time point. The results of this implantation study showed that COAPTIUM CONNECT can achieve nerve repair and regeneration, progressive muscle reinnervation, and functional recovery with no signs of neurotoxicity or separation or migration of the device from the nerve. In addition, the animal study demonstrated the subject device did not cause any biocompatibility concerns for cytotoxicity or acute systemic toxicity and demonstrated photobiological safety of the TISSIUM LIGHT used in the polymerization of the COAPTIUM CONNECT in vivo on the intended nerves for repair.

BIOCOMPATIBILITY/MATERIALS

Biocompatibility of the COAPTIUM CONNECT has been established according to ISO 10993-1:2018, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.” The endpoints evaluated to support the biocompatibility of the COAPTIUM CONNECT include evaluations for cytotoxicity, sensitization, irritation, acute/subacute systemic toxicity, subchronic/chronic systemic toxicity, carcinogenicity, reproductive/developmental toxicity, pyrogenicity, implantation effects, neurotoxicity, and genotoxicity. Results of this testing demonstrated that the implantable components of the device are safe for permanent contact (> 30 days) exposure and the accessories of the device used during the surgery are safe for limited contact (< 24 hours) exposure.

SHELF LIFE/STERILITY

The 6-month shelf life of the device was demonstrated through polymer stability and packaging testing.

Sterilization validation processes of the COAPTIUM CONNECT are provided below:

Test	Test Method Summary	Results
Aseptic processing validation	Validation method in conformance with ISO 13408-1, "Aseptic processing of health care products – Part 1: General requirements," ISO 13408-2, "Aseptic processing of health care products – Part 2: Sterilizing filtration," and the FDA guidance, "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice."	PASS
Ethylene oxide (EO) sterilization validation	Validation method in conformance with ISO 11135, "Sterilization of healthcare products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices," and AAMI TIR28, "Product adoption and process equivalence for ethylene oxide sterilization."	PASS
EO residues	Validation conducted according to ISO 10993-7, "Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals."	PASS
Gamma sterilization validation	Validation method in conformance with ISO 11137-1, "Sterilization of health care products – Radiation – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices."	PASS

Table 1. Sterilization validation of the sterile COAPTIUM CONNECT components and accessories.

ELECTROMAGNETIC COMPATIBILITY & ELECTRICAL SAFETY

The TISSIUM LIGHT was tested in accordance with the following consensus standards and conformed with the following electromagnetic compatibility (EMC), battery safety, and electrical, mechanical and thermal safety standards:

- AAMI ANSI ES60601-1, "Medical Electrical Equipment - Part 1: General Requirements for Basic Safety and Essential Performance."
- AIM 7351731, "Medical Electrical Equipment and System Electromagnetic Immunity Test for Exposure to Radio Frequency Identification Readers."
- IEC 60601-1-2, "Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Electromagnetic Disturbances - Requirements and Tests."
- IEC 62133-2, "Secondary Cells and Batteries Containing Alkaline or Other Non-acid Electrolytes – Safety Requirements for Portable Sealed Secondary Cells, and for Batteries Made from Them, for Use in Portable Applications – Part 2: Lithium Systems."

MAGNETIC RESONANCE (MR) COMPATIBILITY

MR compatibility testing was not conducted for the COAPTIUM CONNECT because the materials of composition are known to be MR safe. The TISSIUM LIGHT is labeled as "MR Unsafe."

Performance Testing

Handling/Ease of Use Validation

A human factors/usability evaluation was conducted to assess user handling and ease of use of the subject device on cadaveric nerves to demonstrate that the COAPTIUM CONNECT can be used by the intended users, for the intended use and under the expected use conditions, without predictable use errors or problems. The study demonstrated that there were no critical use-related errors and that the current Instructions for Use are sufficient to enable successful implantation of COAPTIUM CONNECT. The ease of use of the COAPTIUM CONNECT system was found satisfactory based on positive feedback from the participating surgeons.

Bench Testing

The following bench tests were conducted to demonstrate that the COAPTIUM CONNECT performs as intended. Results from these tests indicated that the device is able to adequately resist external forces expected under clinical use conditions. Results from this testing also support the ability of the TISSIUM LIGHT to adequately cross-link the polymer with limited heat generation.

Testing	Results
Crosslinking efficiency testing using Fourier transform infrared spectroscopy (FTIR) and photo-differential scanning calorimetry (DSC)	PASS
Tensile strength testing	PASS
In vitro degradation testing of polymerized COAPTIUM polymer and coaptation chamber	Adequate physical integrity
Physical dimensions testing of COAPTIUM CONNECT components	PASS
Pull-off strength testing in rabbit nerves	PASS
Repeated compression testing	PASS
COAPTIUM polymer analytical testing and viscosity testing	PASS
Characterization of the heat generated by the photo-polymerization	Negligible heat generated under clinically relevant use conditions
Optical properties of TISSIUM LIGHT (wavelength, intensity)	PASS
Electrical properties of TISSIUM LIGHT (duty cycles, electrical safety and compatibility)	PASS
Mechanical integrity of the TISSIUM LIGHT cover	PASS

Table 2. Performance bench tests conducted on the COAPTIUM CONNECT and TISSIUM LIGHT.

Cadaver Testing

The following tests were conducted in cadaver models to demonstrate that the COAPTIUM CONNECT performs as intended. Results from these tests indicated that the device is able to adequately resist external forces expected during clinical use conditions.

Testing	Results
Pull-off strength testing in human cadaver nerves	PASS
Simulated post-operative force testing	PASS

Table 3. Summary of assessments evaluated in the human cadaver testing of the COAPTIUM CONNECT.

SUMMARY OF CLINICAL INFORMATION

No clinical studies were evaluated assessing the safety and effectiveness of the COAPTIUM CONNECT with TISSIUM LIGHT in support of this De Novo request.

Pediatric Extrapolation

In this De Novo request, existing clinical data was not leveraged to support the use of the device in a pediatric patient population.

LABELING

The labeling includes instructions for use for the physician and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The labeling also includes:

- Detailed description of the device technical parameters and all components.
- Detailed instructions on proper device preparation and implantation.
- Device shelf life.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of an in situ polymerizing peripheral nerve repair device and the measures necessary to mitigate these risks.

Risks to Health	Mitigation Measures
Failed repair due to device failure or user error, leading to delayed and compromised, complicated, or precluded secondary management procedure	In vivo performance testing Human factors/usability testing Non-clinical performance testing Labeling
Adverse tissue reaction	Biocompatibility evaluation Polymerization process characterization In vivo performance testing
Tissue injury	In vivo performance testing

	Polymerization process characterization Non-clinical performance testing Labeling
Infection	Sterilization validation Shelf life testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the in situ polymerizing peripheral nerve repair device is subject to the following special controls:

(1) In vivo performance testing in a clinically relevant model and defect size must demonstrate that the device performs as intended for the repair of peripheral nerve injuries and assess device preparation and deliverability, tissue reactions to the device or degradation products, device migration, and all adverse effects.

(2) A characterization of the following chemical characteristics of the polymerization process must describe how the in situ application of the precursor materials will result in a consistent final device. All physico-chemically relevant changes to parts (iii)-(vi) below are determined to significantly affect the safety or effectiveness of the device (21 CFR 807.81(a)(3)(i)) and must be described in a premarket notification:
   - (i) The technical specifications of the precursor materials and polymerization initiators including the chemical formulation, chemical analysis, appearance, and physical characteristics;
   - (ii) The delivery mechanism of the precursor materials to the site of application;
   - (iii) The polymerization mechanism and polymer structure;
   - (iv) The intermediates or side products produced;
   - (v) The degradation pathway and degradants; and
   - (vi) The contribution of any initiators or quenchers to the polymer, intermediates or side products, and degradants.

(3) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be evaluated:
   - (i) Characterization of the polymerized final device must be performed. Physico-chemically relevant changes to the characteristics below are determined to significantly affect the safety or effectiveness of the device (21 CFR 807.81(a)(3)(i)) and must be described in a premarket notification:
      - (A) The polymerization mechanism and polymer structure;
      - (B) The intermediates or side products produced;
      - (C) The degradation pathway and degradants; and
      - (D) The contribution of any initiators or quenchers to the polymer, intermediates or side products, and degradants.
   - (ii) Mechanical integrity testing, including elastic modulus, compression, swelling, and rebound testing, must be performed.

(iii) Physico-chemical testing of the polymerized device including dimensions, chemical analysis, and reaction temperature must be performed.
(iv) Device deliverability testing with any applicator(s), initiator(s), or delivery system(s) must be performed.

(4) Human factors/usability testing must demonstrate that the intended user(s) in the intended use environment can correctly and safely use the device following the instructions for use.

(5) The tissue-contacting components of the precursor materials, intermediate or side products, degradants, and final polymerized device must be demonstrated to be biocompatible.

(6) Performance data must demonstrate the sterility of all tissue-contacting components of the device and any delivery systems.

(7) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(8) Labeling must include:
(i) Instructions on proper device preparation and implantation;
(ii) Description of the device technical parameters and all components; and
(iii) A shelf life.

BENEFIT-RISK DETERMINATION

The risks of the device are based on non-clinical laboratory and animal studies described above. The risks associated with the use of the COAPTIUM CONNECT and TISSIUM LIGHT include adverse tissue reactions, infection, tissue injury, device failure, and use error. All risks have been mitigated through the performance testing.

The totality of evidence presented in the De Novo request supports the conclusion that COAPTIUM CONNECT with TISSIUM LIGHT provide meaningful clinical benefits to the patient population with peripheral nerve injuries that are not in continuity. Benefits have been demonstrated through the use of both animal and cadaver studies to demonstrate the utility of using COAPTIUM CONNECT for the sutureless repair of peripheral nerves not in continuity and the ability of the device to facilitate long-term nerve repair and regeneration. Valid scientific data from the animal studies has demonstrated that the subject device meets the safety and functional requirements to achieve the proposed intended use by demonstrating recovery of sensory and motor responses and recovery of innervated muscle mass with histopathology demonstrating nerve regeneration. Based upon the animal study data and the rate of peripheral nerve regeneration published in the clinical literature[1,2], the benefits outweigh the risks to health for the COAPTIUM CONNECT with TISSIUM LIGHT for the indicated use of sutureless repair of peripheral nerve injuries not in continuity in which a gap closure ≤ 1 cm is present or can be achieved with flexion of the extremity.

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[1] A. Höke, *J Clin Invest*. 2011; 121(11):4231-4234. Doi:10.1172/JC159320.
[2] H.J. Seddon, P.B. Medawar, H. Smith, *J. Physiol*. 1943; 102: 191-215.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> COAPTIUM CONNECT with TISSIUM LIGHT is indicated for the sutureless repair of peripheral nerve injuries not in continuity in which a gap closure $\leq$ 1 cm is present or can be achieved with flexion of the extremity.

The probable benefits outweigh the probable risks of the COAPTIUM CONNECT with TISSIUM LIGHT. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the COAPTIUM CONNECT with TISSIUM LIGHT is granted and the device is classified as follows:

Product Code: SFD
Device Type: In situ polymerizing peripheral nerve repair device
Regulation Number: 21 CFR 882.5270
Class: II